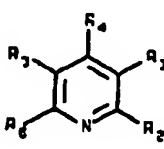




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 213/80, 213/81, 213/83, 409/12, 417/04, 413/04, 409/04, 407/04, 401/12, A61K 31/44</p>	A1	<p>(11) International Publication Number: WO 99/41237</p> <p>(43) International Publication Date: 19 August 1999 (19.08.99)</p>
<p>(21) International Application Number: PCT/US99/01871</p> <p>(22) International Filing Date: 11 February 1999 (11.02.99)</p> <p>(30) Priority Data: 60/074,586 13 February 1998 (13.02.98) US</p> <p>(71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): LEE, Len, F. [-/US]; St. Charles, MO (US). GLENN, Kevin, C. [US/US]; Maryland Heights, MO (US). CONNOLLY, Daniel, T. [US/US]; Ballwin, MO (US). CORLEY, David, G. [US/US]; St. Louis, MO (US). FLYNN, Daniel, L. [US/US]; Clarkson Valley, MO (US). HAMME, Ashton [-/-]; * (**). HEGDE, Shridhar, G. [-/US]; Ballwin, MO (US). MELTON, Michele, A. [-/US]; Bridgeton, MO (US). SCHILLING, Roger, J. [-/US]; St. Louis, MO (US). SIKORSKI, James, A. [US/US]; * (**). WALL, Nancy, N. [US/US]; Florissant, MO (US). ZABLOCKI, Jeffrey, A. [US/US]; Lafayette, CO (US).</p>		<p>(74) Agents: WILLIAMS, Roger, A. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: SUBSTITUTED PYRIDINES USEFUL FOR INHIBITING CHOLESTERYL ESTER TRANSFER PROTEIN ACTIVITY</p> <div style="text-align: center; margin: 20px 0;">  <p>(IA)</p> </div> <p>(57) Abstract</p> <p>A class of substituted pyridines which are useful for inhibiting the activity of cholesteryl ester transfer protein and have the structural formula (IA) wherein: R₂, R₃, R₄, R₅, R₆, are defined in the claims.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**Substituted Pyridines Useful for Inhibiting
Cholesteryl Ester Transfer Protein Activity**

Field of the Invention

This invention is in the field of preventing and/or
5 treating cardiovascular disease, and specifically relates
to compounds, compositions and methods for preventing
and/or treating atherosclerosis and other coronary artery
disease. More particularly, the invention relates to
substituted pyridine compounds that inhibit cholesteryl
10 ester transfer protein (CETP), also known as plasma lipid
transfer protein-I.

Background of the Invention

Numerous studies have demonstrated that a low plasma
concentration of high density lipoprotein (HDL)
15 cholesterol is a powerful risk factor for the development
of atherosclerosis (Barter and Rye, *Atherosclerosis*, 121,
1-12 (1996)). HDL is one of the major classes of
lipoproteins that function in the transport of lipids
through the blood. The major lipids found associated
20 with HDL include cholesterol, cholesteryl ester,
triglycerides, phospholipids and fatty acids. The other
classes of lipoproteins found in the blood are low
density lipoprotein (LDL) and very low density
lipoprotein (VLDL). Since low levels of HDL cholesterol
25 increase the risk of atherosclerosis, methods for
elevating plasma HDL cholesterol would be therapeutically
beneficial for the treatment of atherosclerosis and other
diseases associated with accumulation of lipid in the
blood vessels. These diseases include, but are not
30 limited to, coronary heart disease, peripheral vascular
disease, and stroke.

Atherosclerosis underlies most coronary artery
disease (CAD), a major cause of morbidity and mortality
in modern society. High LDL cholesterol (above 180

mg/dl) and low HDL cholesterol (below 35 mg/dl) have been shown to be important contributors to the development of atherosclerosis. Other diseases, such as peripheral vascular disease, stroke, and hypercholesterolaemia are negatively affected by adverse HDL/LDL ratios. Inhibition of CETP by the subject compounds are shown to effectively modify plasma HDL/LDL ratios, and to check the progress and/or formation of these diseases.

CETP is a plasma protein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood (Tall, *J. Lipid Res.*, 34, 1255-74 (1993)). The movement of cholesteryl ester from HDL to LDL by CETP has the effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile (McCarthy, *Medicinal Res. Revs.*, 13, 139-59 (1993)). This exact phenomenon was first demonstrated by Swenson et al., (*J. Biol. Chem.*, 264, 14318 (1989)) with the use of a monoclonal antibody that specifically inhibited CETP. In rabbits, the antibody caused an elevation of the plasma HDL cholesterol and a decrease in LDL cholesterol. Son et al. (*Biochim. Biophys. Acta* 795, 743-480 (1984)) describes proteins from human plasma that inhibit CETP. U.S. Patent 5,519,001, issued to Kushwaha et al., describes a 36 amino acid peptide derived from baboon apo C-1 that inhibits CETP activity.

There have been several reports of compounds that act as CETP inhibitors. Barrett et al. (*J. Am. Chem. Soc.*, 118, 7863-63 (1996)) describes cyclopropane-containing CETP inhibitors. Pietzonka et al. (*Bioorg. Med. Chem. Lett.*, 6, 1951-54 (1996)) describe phosphonate-containing analogs of cholesteryl ester as CETP inhibitors. Coval et al. (*Bioorg. Med. Chem. Lett.*, 5, 605-610 (1995)) describe Wiedendiol-A and -B, and

related sesquiterpene compounds, as CETP inhibitors. Lee et al. (*J. Antibiotics*, 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids*, 25, 216-220, (1990)) describe cholesteryl acetyl
5 bromide as a CETP inhibitor. Morton and Zilversmit (*J. Lipid Res.*, 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Bisgaier et al. (*Lipids*, 29, 811-8 (1994)) describe 4-phenyl-5-
10 tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor.

A number of substituted pyridine compounds are known. For example, U.S. Patents 4,609,399, 4,655,816; 4,692,184; 4,698,093; 4,789,395; 4,885,026; 4,936,905; 4,988,384; 5,037,469; 5,125,961; 5,129,943; 5,156,670;
15 5,169,432; and 5,260,262 each disclose novel substituted pyridines which are useful as herbicides and herbicide intermediates. No pharmacologic properties for the substituted pyridines are recited in these patents. Except as set forth below, the literature does not
20 describe substituted pyridines as inhibitors of CETP.

Connolly et al. (*Biochem. Biophys. Res. Comm.* 223, 42-47 (1996)), describe 4,4'-dithiopyridine, 2,2'-dithiopyridine, 6,6'-dithionicotinic acid and 2,2'-dithiobis (pyridine-N-oxide) as CETP inhibitors. The
25 isolated pyridine compounds tested by Connolly et al. were, at best, inhibitory only after a 16 hour pre-incubation period and would not be useful in situations requiring rapid and potent inhibition. Connolly et al. also neither addressed whether substitution of the
30 reported pyridines would increase their potency nor suggested the testing or use of specific substituted pyridines.

European Patent Application 796 846 A1 describes certain 2-aryl-substituted pyridines for use in the
35 treatment of lipoproteinaemia and hyperlipoproteinaemia.

European Patent Application 818 197 A1 describes

certain 2-aryl-substituted pyridines for use in the treatment of hyperlipoproteinaemia and atherosclerosis.

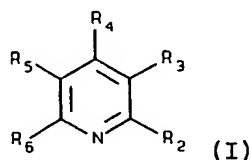
U.S. Patent 4,925,852 describes 3-demethylmevalonic acid derivatives for use as inhibitors of cholesterol biosynthesis.

U.S. Patent 5,169,857 describes 7-(polysubstituted pyridyl)-hept-6-enates for use in the treatment of hyperproteinaemia, lipoproteinaemia or arteriosclerosis.

WO 98/04528 describes certain 4-aryl-pyridyl compounds as anti-hypercholesterolemic, anti-hyperlipoproteinemic and anti-hyperglycemic agents.

Summary of the Invention

The present invention is directed to a method for administering to a subject a therapeutically effective amount of a substituted pyridine of Formula I:



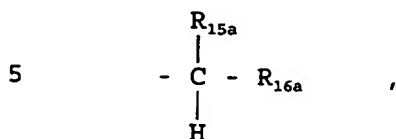
wherein:

R₂ and R₆ are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of R₂ and R₆ is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R₃ is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,

-CHO,

-CO₂R₇, wherein R₇ is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and



wherein R_{15a} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy, and

R_{16a} is selected from the group consisting of alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heteroaryl, and heterocyclyl, arylalkoxy, trialkylsilyloxy;

R₄ is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy, heteroaroxyloxy, heterocyclyloyloxy, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, heterocyclyloxycarbonyl, thio, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl,

heterocyclylthioalkenyl, alkylamino, alkenylamino,
 alkynylamino, arylamino, heteroarylamino,
 heterocyclylamino, aryldialkylamino, diarylamino,
 diheteroarylamino, alkylarylamine, alkylheteroarylamine,
 5 arylheteroarylamine, trialkylsilyl, trialkenylsilyl,
 triarylsilyl,

-OC(O)N(R_{8a}R_{8b}), wherein R_{8a} and R_{8b} are
 independently selected from the group consisting of
 alkyl, alkenyl, alkynyl, aryl, heteroaryl and
 10 heterocyclyl,

-SO₂R₉, wherein R₉ is selected from the group
 consisting of hydroxy, alkyl, alkenyl, alkynyl,
 aryl, heteroaryl and heterocyclyl,

-OP(O)(OR_{10a})(OR_{10b}), wherein R_{10a} and R_{10b} are
 15 independently selected from the group consisting of
 hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl, and

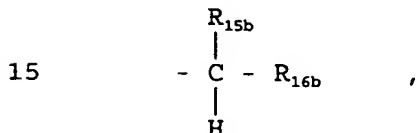
-OP(S)(OR_{11a})(OR_{11b}), wherein R_{11a} and R_{11b} are
 independently selected from the group consisting of
 20 alkyl, alkenyl, alkynyl, aryl, heteroaryl and
 heterocyclyl;

R₅ is selected from the group consisting of hydrogen,
 hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl,
 cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl,
 25 heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy,
 aryloxy, heteroaryloxy, heterocycliloxy,
 alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl,
 alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl,
 heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl,
 30 cycloalkylalkyl, cycloalkenylalkyl, aralkyl,
 heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl,
 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
 heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl,
 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
 35 heteroarylthioalkyl, heterocyclylthioalkyl,

alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,
 arylthioalkenyl, heteroarylthioalkenyl,
 heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl,
 alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl,
 5 heterocyclyloxyalkyl, alkoxyalkenyl, alkenoxyalkenyl,
 alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl,
 heterocyclyloxyalkenyl, cyano,
 hydroxymethyl,

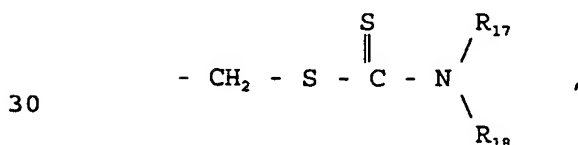
-CO₂R₁₄,

10 wherein R₁₄ is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl;



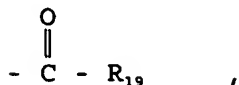
wherein R_{15b} is selected from the group
 consisting of hydroxy, hydrogen, halogen, alkylthio,
 20 alkenylthio, alkynylthio, arylthio, heteroarylthio,
 heterocyclylthio, alkoxy, alkenoxy, alkynoxy,
 aryloxy, heteroaryloxy, heterocyclyloxy, aroyloxy,
 and alkylsulfonyloxy, and

R_{16b} is selected from the group consisting of
 25 alkyl, alkenyl, alkynyl, aryl, heteroaryl,
 heterocyclyl, arylalkoxy, and trialkylsilyloxy;



wherein R₁₇ and R₁₈ are independently selected
 from the group consisting of alkyl, cycloalkyl,

alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



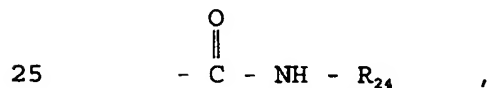
5 wherein R_{19} is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{SR}_{20}$, $-\text{OR}_{21}$, and $-\text{R}_{22}\text{CO}_2\text{R}_{23}$, wherein

10 R_{20} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminoaryl, aminoheteroaryl, aminoheterocyclyl, alkylheteroarylamino, arylheteroarylamino,

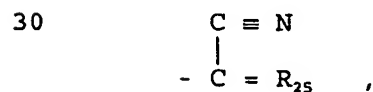
15 R_{21} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl,

R_{22} is selected from the group consisting of alkylene or arylene, and

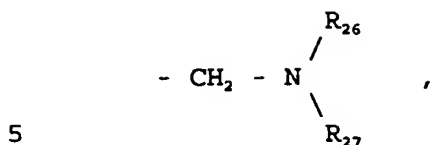
20 R_{23} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



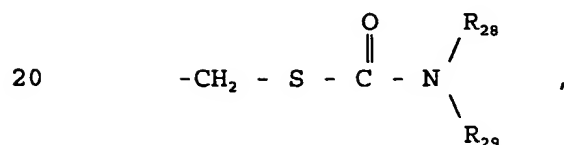
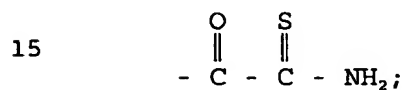
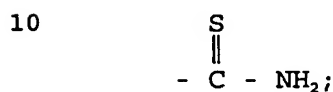
25 wherein R_{24} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, aralkenyl, and aralkynyl;



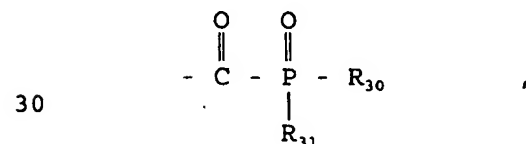
30 wherein R_{25} is heterocyclylidenyl;



wherein R_{26} and R_{27} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

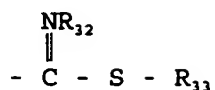


25 wherein R_{28} and R_{29} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

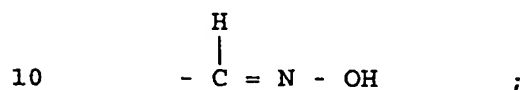


wherein R_{30} and R_{31} are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocyclyloxy; and

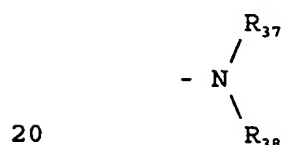
10



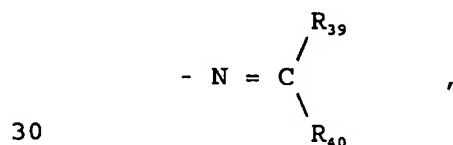
5 wherein R_{32} and R_{33} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



15 wherein R_{36} is selected from the group consisting of alkyl, alkenyl, aryl, heteroaryl and heterocyclyl;



25 wherein R_{37} and R_{38} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



35 wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclthio, and

R_{40} is selected from the group consisting of

11

haloalkyl, haloalkenyl, haloalkynyl, haloaryl,
 haloheteroaryl, haloheterocyclyl, cycloalkyl,
 cycloalkenyl, heterocyclalkoxy,
 heterocyclalkenoxy, heterocyclalkynoxy,
 5 alkylthio, alkenylthio, alkynylthio, arylthio,
 heteroarylthio and heterocyclthio;

- N = R₄₁,

wherein R₄₁ is heterocyclidenyl;

10
$$- \text{NR}_{42} - \overset{\text{O}}{\parallel} \text{C} - \text{R}_{43} \quad ,$$

wherein R₄₂ is selected from the group
 consisting of hydrogen, alkyl, alkenyl, alkynyl,
 aryl, heteroaryl, and heterocyclyl, and

15 R₄₃ is selected from the group consisting of
 hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl,
 heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl,
 haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl,
 and haloheterocyclyl;

20
$$- \text{NH} - \overset{\text{O}}{\parallel} \text{C} - \text{NH} - \text{R}_{44} \quad ,$$

wherein R₄₄ is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 25 alkynyl, aryl, heteroaryl and heterocyclyl;

- N = S = O;

- N = C = S;

- N = C = O;

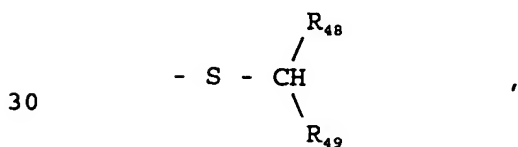
- N₃;

- SR₄₅ ,

wherein R₄₅ is selected from the group
 consisting of hydrogen, alkyl, alkenyl, alkynyl,
 aryl, heteroaryl, heterocyclyl, haloalkyl,
 5 haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl,
 haloheterocyclyl, heterocyclyl, cycloalkylalkyl,
 cycloalkenylalkyl, aralkyl, heteroarylalkyl,
 heterocyclylalkyl, cycloalkylalkenyl,
 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
 10 heterocyclylalkenyl, alkylthioalkyl,
 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
 heteroarylthioalkyl, heterocyclylthioalkyl,
 alkylthioalkenyl, alkenylthioalkenyl,
 alkynylthioalkenyl, arylthioalkenyl,
 15 heteroarylthioalkenyl, heterocyclylthioalkenyl,
 aminocarbonylalkyl, aminocarbonylalkenyl,
 aminocarbonylalkynyl, aminocarbonylaryl,
 aminocarbonylheteroaryl, and
 aminocarbonylheterocyclyl,
 20 -SR₄₆, and -CH₂R₄₇,

wherein R₄₆ is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl, and

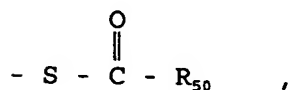
R₄₇ is selected from the group consisting of
 25 hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl
 and heterocyclyl; and



wherein R₄₈ is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 alkynyl, aryl, heteroaryl and heterocyclyl, and
 35 R₄₉ is selected from the group consisting of

alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl;

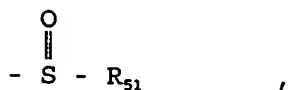
5



wherein R_{50} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy;

10

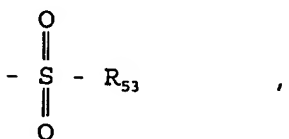
15



wherein R_{51} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and

20

25



wherein R_{53} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

or a pharmaceutically acceptable salt or tautomer thereof,

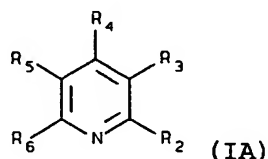
30

provided that when R_5 is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, then the heterocyclyl radical of the corresponding

heterocyclalkyl or heterocyclalkenyl is other than a δ -lactone; and

provided that when R_4 is aryl, heteroaryl or heterocycl, and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.

In another embodiment, the method involves the administration of a therapeutically effective amount of a substituted pyridine of Formula IA wherein:

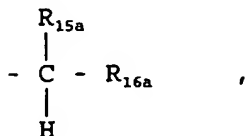


R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, chlorofluorinated alkyl, cycloalkyl, heterocycl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,

$-\text{CO}_2R_7$,

wherein R_7 is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and



wherein R_{15a} is selected from the group

15

consisting of hydroxy, halogen, alkylthio and alkoxy, and

R_{16a} is selected from the group consisting of alkyl, aryl and heteroaryl;

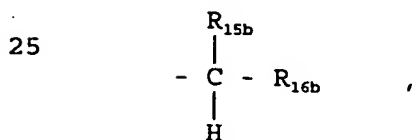
- 5 R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio,
- 10 cycloalkylthio, heterocyclylthio, alkylthioalkyl, alkylamino, trialkylsilyl,
- OC(O)N(R_8)₂, wherein R_8 is aryl,
- SO₂ R_9 , wherein R_9 is aryl,
- OP(O)(OR_{10})₂, wherein R_{10} is alkyl, and
- 15 -OP(S)(OR_{11})₂, wherein R_{11} is alkyl;

R_5 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, haloalkyl, alkynyl, heterocyclyl, heteroaryl, alkoxy, aryloxy, arylcarbonyloxyalkyl, heterocyclylalkyl, alkylthioalkyl,

20 arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, cyano, hydroxymethyl,

-CO₂ R_{14} ,

wherein R_{14} is alkyl;



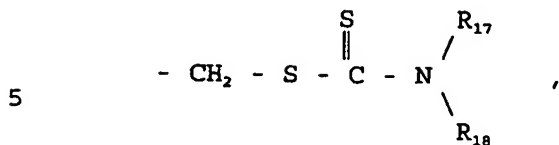
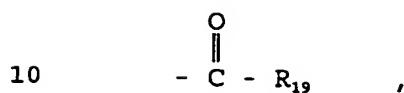
wherein R_{15b} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio and alkoxy, and

30

R_{16b} is selected from the group consisting of

16

alkyl, aryl and heteroaryl;

wherein R_{17} and R_{18} are independently alkyl;

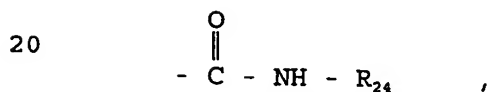
wherein R_{19} is selected from the group consisting of aryl, heteroaryl, $-\text{SR}_{20}$, $-\text{OR}_{21}$, and $-\text{R}_{22}\text{CO}_2\text{R}_{23}$,

15 wherein R_{20} is selected from the group consisting of alkyl, aryl and aminoalkyl,

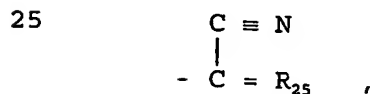
R_{21} is aryl,

R_{22} is alkylene, and

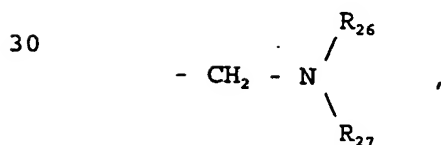
R_{23} is alkyl;



wherein R_{24} is selected from the group consisting of hydrogen, unsubstituted alkyl, and aralkyl;

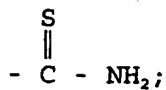


wherein R_{25} is heterocyclylidenyl;

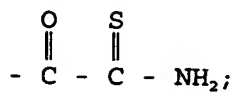


17

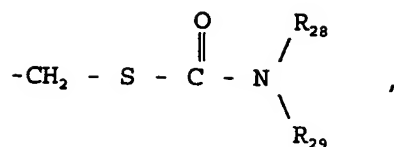
wherein R_{26} and R_{27} are independently alkyl;



5

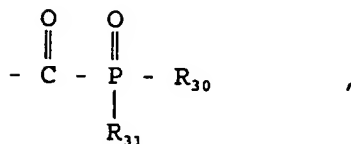


10



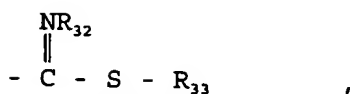
wherein R_{28} and R_{29} are independently alkyl;

15



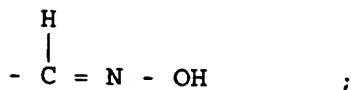
20

wherein R_{30} and R_{31} are independently alkoxy;

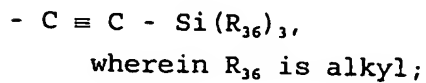


25

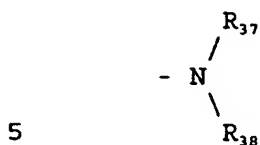
wherein R_{32} is selected from the group consisting of hydrogen and alkyl, and R_{33} is alkyl;



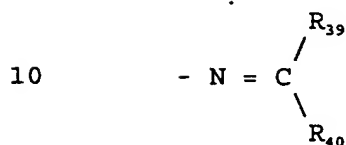
30



18



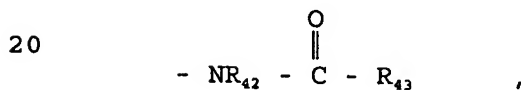
wherein R_{37} and R_{38} are independently alkyl;



wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and

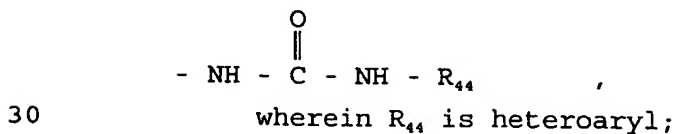
15 R_{40} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclylalkoxy, and alkylthio;

- $\text{N} = \text{R}_{41}$, wherein R_{41} is heterocyclidenyl;



wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and

25 R_{43} is selected from the group consisting of cycloalkyl, chlorinated alkyl and substituted heteroaryl;



- $\text{N} = \text{S} = \text{O}$;

- $\text{N} = \text{C} = \text{S}$;

- N = C = O;

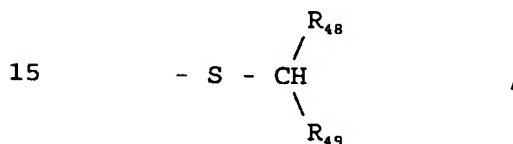
- N₃;

- SR₄₅ ,

5 wherein R₄₅ is selected from the group consisting of hydrogen, alkyl, haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, alkylthioalkyl, aminocarbonylalkyl, -SR₄₆, and -CH₂R₄₇,

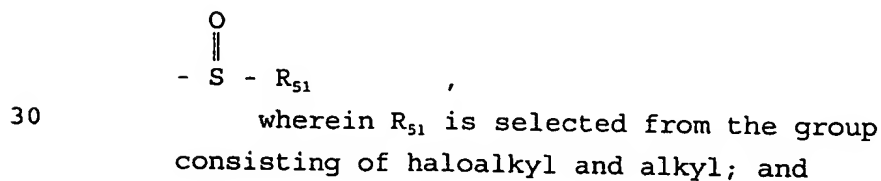
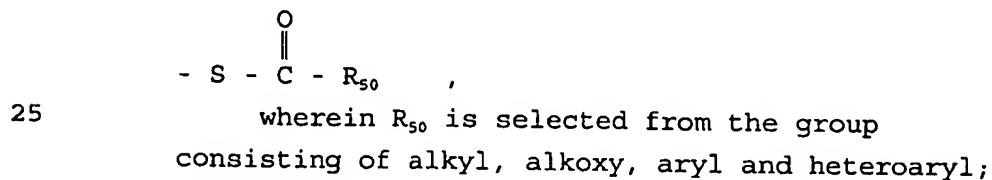
10 wherein R₄₆ is selected from the group consisting of aryl and heteroaryl, and

R₄₇ is selected from the group consisting of aryl and heteroaryl; and

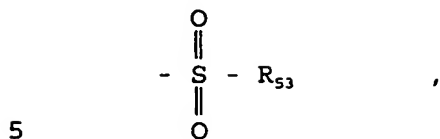


20 wherein R₄₈ is selected from the group consisting of hydrogen and alkyl, and

R₄₉ is selected from the group consisting of alkoxy and haloalkyl;



20



wherein R_{53} is aryl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_5 is heterocyclalkyl or
 10 heterocyclalkenyl, then the heterocycl radical is other than a δ -lactone and the alkyl or alkenyl radical is other than $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}=\text{CH}-$.

Preferably, the immediately preceding embodiment involves the administration of a substituted pyridine of
 15 Formula IA as described above wherein:

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is $-\overset{\text{O}}{\parallel}\text{C}-\text{R}_{19}$,
 R_6 is trifluoromethyl and R_{19} is the heteroaryl 1-
 20 pyrazolyl, then R_4 is other than isopropylamino; and

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is the unsubstituted heterocycl 2-(4,5-dihydro-oxazolyl), and R_6 is trifluoromethyl, then R_4 is other than cyclopropylmethyl; and

25 when R_2 and R_6 are selected from the group consisting of difluoromethyl and trifluoromethyl, R_3 is selected from the group consisting of $-\text{CO}_2\text{H}$ and $-\text{CO}_2\text{C}_2\text{H}_5$, and R_5 is cyano, then R_4 is other than ethyl or $-\text{CH}=\text{C}(\text{CH}_3)_2$; and

30 when R_2 is methyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is $-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{R}_{24}$, R_6 is methyl, and R_{24} is $-\text{C}(\text{O})\text{NHCH}_2-$ (4-chlorophenyl), then R_4

is other than hydrogen; and

when R_2 is methyl, R_3 and R_5 are $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is i-propoxy, then R_6 is other than methyl; and

5 when R_2 is difluoromethyl, R_4 is $-\text{CH}=\text{C}(\text{CH}_3)_2$, R_5 is $-\text{CO}_2\text{CH}_3$, and R_6 is trifluoromethyl, then R_3 is other than $-\text{CO}_2\text{H}$; and

when R_2 is methyl, R_4 is hydrogen, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is methyl, then R_3 is other than $-\text{CO}_2\text{C}_2\text{H}_5$;

10 when R_2 is difluoromethyl, R_4 is hydrogen, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is other than $-\text{CO}_2\text{C}_2\text{H}_5$;

when R_2 is difluoromethyl, R_4 is $-\text{CH}_2\text{SCH}_3$, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is other than $-\text{CO}_2\text{H}$;

15 when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_4 is isobutyl, R_5 is $-\text{CO}_2\text{CH}_3$, then R_6 is other than methyl;

20 when R_2 is difluoromethyl, R_4 is selected from the group consisting of isopropyl and isobutyl, R_5 is $-\text{CO}_2\text{R}_{14}$, R_6 is trifluoromethyl, and R_{14} is alkyl, then R_3 is other than amido;

when R_2 is selected from the group consisting of hydroxy and trifluoromethyl, R_4 and R_5 are hydrogen, and R_6 is selected from the group consisting of methyl and trifluoromethyl, then R_3 is other than $-\text{CO}_2\text{H}$;

25 when R_2 is selected from the group consisting of methyl, difluoromethyl and trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is hydrogen, and R_6 is selected from the group

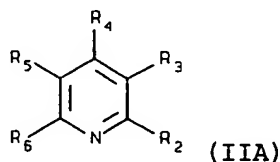
consisting of methyl and trifluoromethyl, then R_4 is other than alkyl or arylcarbonyloxy;

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydroxy, and R_5 is hydrogen, then R_6 is other than
5 hydrogen; and

when R_2 is trifluoromethyl, R_3 is selected from the group consisting of $-\text{CO}_2\text{H}$ and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is methyl, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is other than hydroxy.

10 Among the objects of the present method are the inhibition of CTEP in vivo; the treatment or prevention of coronary artery disease; the treatment or prevention of atherosclerosis; the alteration of the LDL/HDL ratio or profile in plasma; and the elevation of HDL levels in
15 plasma.

The present invention is additionally directed to the novel substituted pyridines of Formula IIA:



wherein:

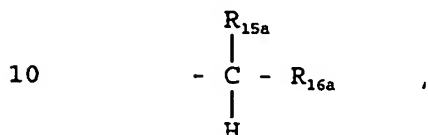
20 R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least
25 one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, hydroxymethyl, arylalkoxyalkyl, trialkylsilyloxyalkyl,

-CHO,

5 -CO₂R₇,

wherein R₇ is selected from the group consisting of hydrogen and alkyl; and



wherein R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, and

15 R_{16a} is selected from the group consisting of alkyl, haloalkyl, alkenyl, aryl and heteroaryl;

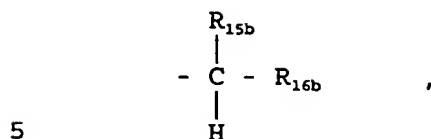
R₄ is selected from the group consisting of hydrogen, hydroxy, alkyl, aryl, cycloalkyl, cycloalkylalkyl, 20 heteroarylalkyl, alkoxy, thio, trialkylsilyl, alkylamino, and -OC(O)N(R₈)₂, wherein R₈ is aryl;

R₅ is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aralkyl, alkoxy, aryloxy, 25 cycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, arylcarbonyloxyalkyl, pyrrolyl, substituted pyrrolidinyl, hydroxymethyl, arylalkoxyalkyl, and trialkylsilyloxyalkyl,

30 - CO₂R₁₄,

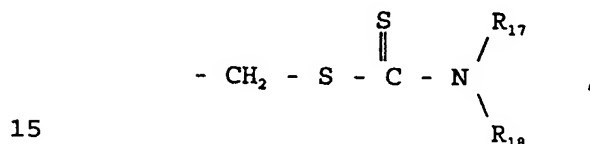
wherein R₁₄ is alkyl;

24

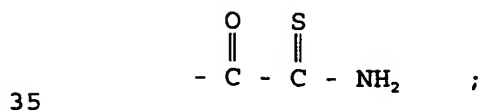
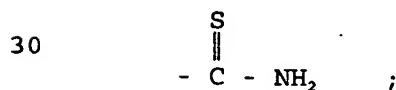
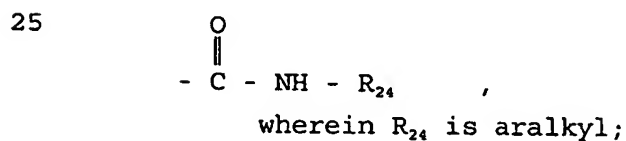
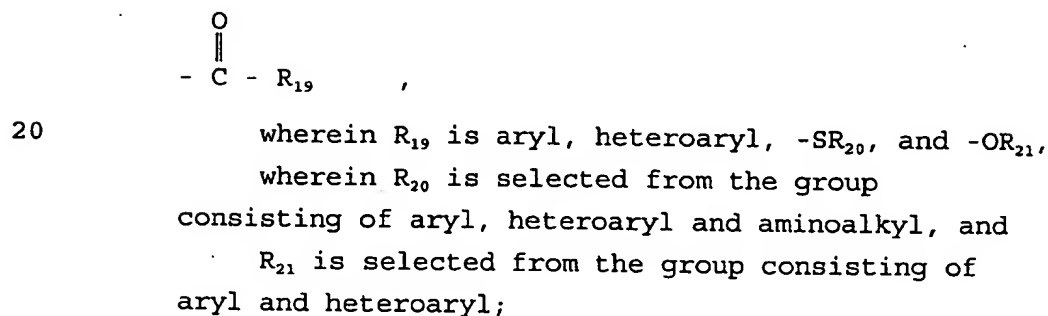


wherein R_{15b} is selected from the group consisting of hydroxy, halogen, alkoxy, and alkylthio, aryloxy, and alkylsulfonyloxy, and

10 R_{16b} is selected from the group consisting of alkyl, alkenyl, aryl, and heteroaryl;

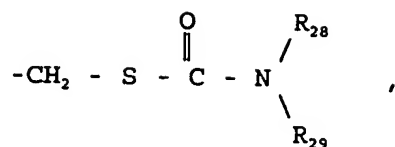


wherein R_{17} and R_{18} are independently alkyl;



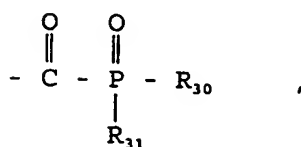
25

5

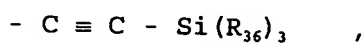


wherein R_{28} and R_{29} are independently alkyl;

10

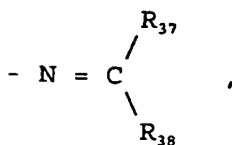


wherein R_{30} and R_{31} are independently alkoxy;



wherein R_{36} is alkyl;

15



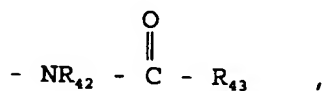
20

wherein R_{37} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclylalkoxy, and alkylthio;

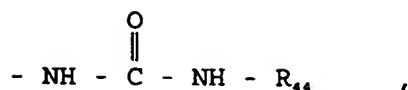
25

provided that when R_{37} is hydrogen, then R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclylalkoxy;

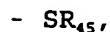
30



wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and R_{43} is substituted heteroaryl;



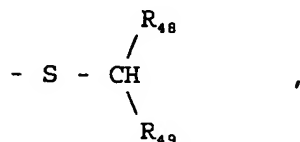
5 wherein R_{44} is selected from the group
consisting of aryl and heteroaryl;



 wherein R_{45} is selected from the group
consisting of haloalkyl, heterocyclyl,
alkylthioalkyl, aminocarbonylalkyl, $-\text{SR}_{46}$, and
10 $-\text{CH}_2\text{R}_{47}$,

 wherein R_{46} is selected from the group
consisting of aryl and heteroaryl, and

R_{47} is selected from the group consisting of
methylenedioxyphenyl, pyridyl, quinolinyl,
15 tetrahydronaphthyl and benzodioxanyl;

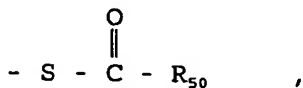


20

 wherein R_{48} is selected from the group
consisting of hydrogen and alkyl, and

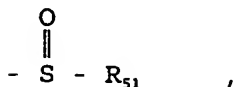
R_{49} is selected from the group consisting of
alkoxy and haloalkyl;

25



 wherein R_{50} is selected from the group
consisting of alkyl, alkoxy, and heteroaryl; and

30



 wherein R_{51} is haloalkyl;

or a pharmaceutically acceptable salt or tautomer

thereof,

provided that:

when R_2 is selected from the group consisting of difluoromethyl and trifluoromethyl, R_3 is selected from the group consisting of $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$ and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is hydrogen, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is other than hydrogen, hydroxy or iso-butyl; provided further that when R_2 , R_3 and R_5 are as defined above, and R_4 is selected from the group consisting of alkylamino and alkoxy, then R_6 is hydrogen;

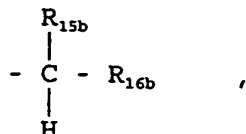
when R_2 is selected from the group consisting of fluorinated methyl and chlorofluorinated methyl, R_3 is selected from the group consisting of hydroxymethyl and CO_2R_7 , R_5 is selected from the group consisting of hydroxymethyl and CO_2R_{14} , R_6 is selected from the group consisting of alkyl, fluorinated methyl and chlorofluorinated methyl, and R_7 and R_{14} are independently alkyl, then R_4 is other than alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, alkylamino and heteroarylalkyl;

when R_2 is selected from the group consisting of difluoromethyl and trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydrogen, and R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is other than trifluoromethyl;

when R_2 is trifluoromethyl, R_3 is CO_2R_7 , R_5 is methyl, and R_6 is selected from the group consisting of fluorinated methyl, fluorinated ethyl and chlorofluorinated methyl, then R_4 is other than alkoxy, alkylamino and hydroxy;

when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_3 is $-\text{CO}_2R_7$, and R_7 is alkyl, then R_5 is other than arylcarbonyl, heteroarylcarbonyl or

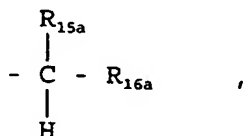
5



10 wherein R_{16b} is alkyl when R_{15b} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16b} is aryl or heteroaryl when R_{15b} is hydroxy;

when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_5 is $-\text{CO}_2R_{14}$, and
15 R_{14} is alkyl, then R_3 is other than arylcarbonyl, heteroarylcarbonyl or

20



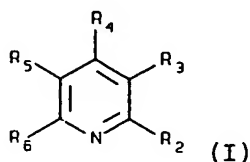
wherein R_{16a} is alkyl when R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16a} is aryl or heteroaryl when R_{15a} is hydroxy; and

25 when R_2 and R_6 are independently selected from fluorinated methyl and chlorofluorinated methyl, R_3 is CO_2R_7 , R_5 is hydroxy, alkoxy or aryloxy, then R_4 is other than hydrogen, hydroxy, alkyl or alkoxy; and

when R_4 is aryl and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.
30

Detailed Description of the Preferred EmbodimentsNovel Methods

The present invention comprises a method for the treatment or prophylaxis of CTEP-mediated disorders (such as coronary artery disease) in a subject, comprising administering to the subject having such a disorder a therapeutically-effective amount of a compound of Formula I:



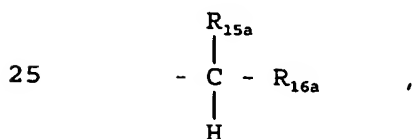
wherein:

R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,

-CHO,

-CO₂R₇, wherein R₇ is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and



wherein R_{15a} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclioxy, and

R_{16a} is selected from the group consisting of alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heteroaryl, and heterocyclyl, arylalkoxy, trialkylsilyloxy;

R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclioxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, aryloyloxy, heteroaroxyloxy, heterocyclioxyloxy, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, heterocyclioxy carbonyl, thio, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, cycloalkylthio, cycloalkenylthio, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkylamino, alkenylamino, alkynylamino, arylamino, heteroarylamino, heterocyclylamino, aryldialkylamino, diarylamino, diheteroarylamino, alkylaryl amino, alkylheteroaryl amino, arylheteroaryl amino, trialkylsilyl, trialkenylsilyl, triarylsilyl,

$-OC(O)N(R_{8a}R_{8b})$, wherein R_{8a} and R_{8b} are

independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl,

5 -SO₂R₉, wherein R₉ is selected from the group consisting of hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl,

-OP(O)(OR_{10a})(OR_{10b}), wherein R_{10a} and R_{10b} are independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

10 -OP(S)(OR_{11a})(OR_{11b}), wherein R_{11a} and R_{11b} are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

15 R₅ is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocycliloxy,

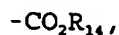
20 alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl,

25 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,

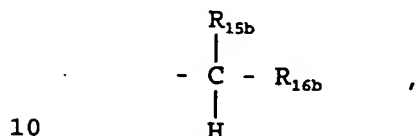
30 arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heterocycliloxyalkyl, alkoxyalkenyl, alkenoxyalkenyl, alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl,

35 heterocycliloxyalkenyl, cyano,

hydroxymethyl,

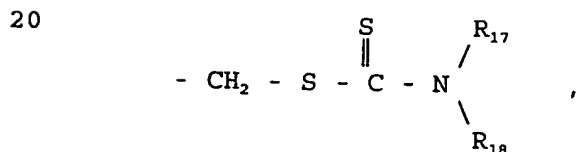


wherein R_{14} is selected from the group
consisting of alkyl, alkenyl, alkynyl, aryl,
5 heteroaryl and heterocyclyl;

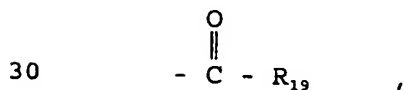


wherein R_{15b} is selected from the group
consisting of hydroxy, hydrogen, halogen, alkylthio,
alkenylthio, alkynylthio, arylthio, heteroarylthio,
heterocyclylthio, alkoxy, alkenoxy, alkynoxy,
15 aryloxy, heteroaryloxy, heterocycliloxy, aroyloxy,
and alkylsulfonyloxy, and

R_{16b} is selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl,
heterocyclyl, arylalkoxy, and trialkylsilyloxy;



wherein R_{17} and R_{18} are independently selected
from the group consisting of alkyl, cycloalkyl,
25 alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



wherein R_{19} is selected from the group
consisting of alkyl, cycloalkyl, alkenyl, alkynyl,

aryl, heteroaryl, heterocyclyl, $-SR_{20}$, $-OR_{21}$, and $-R_{22}CO_2R_{23}$, wherein

5 R_{20} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminoaryl, aminoheteroaryl, aminoheterocyclyl, alkylheteroarylamino, arylheteroarylamino,

10 R_{21} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl,

R_{22} is selected from the group consisting of alkylene or arylene, and

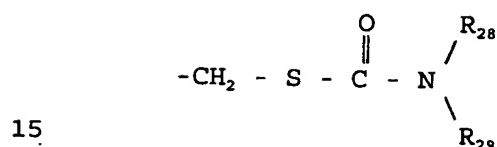
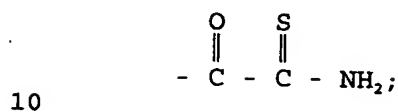
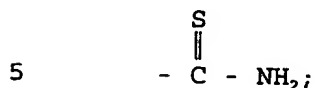
15 R_{23} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

20
$$- \overset{\overset{O}{\parallel}}{C} - NH - R_{24} \quad ,$$
 wherein R_{24} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, aralkenyl, and aralkynyl;

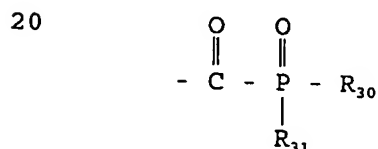
25
$$- \overset{\overset{C \equiv N}{|}}{C} = R_{25} \quad ,$$
 wherein R_{25} is heterocyclylidenyl;

30
$$- CH_2 - N \begin{array}{l} \nearrow R_{26} \\ \searrow R_{27} \end{array} \quad ,$$
 wherein R_{26} and R_{27} are independently selected from the group consisting of hydrogen, alkyl,

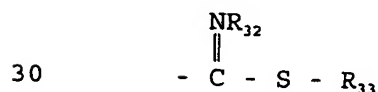
cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



wherein R_{28} and R_{29} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

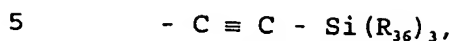
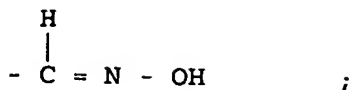


25 wherein R_{30} and R_{31} are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocyclyloxy; and

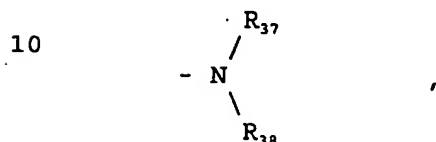


wherein R_{32} and R_{33} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

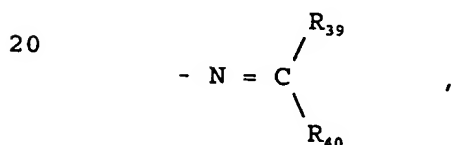
35



wherein R_{36} is selected from the group consisting of alkyl, alkenyl, aryl, heteroaryl and heterocyclyl;



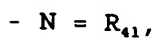
15 wherein R_{37} and R_{38} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



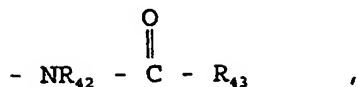
25 wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclloxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio, and

30 R_{40} is selected from the group consisting of haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxy, heterocyclylalkenoxy, heterocyclylalkynoxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio;

35

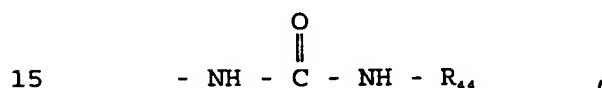


wherein R_{41} is heterocyclylidenyl;

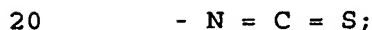
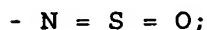


5 wherein R_{42} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, and

R_{43} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, 10 heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, and haloheterocyclyl;



 wherein R_{44} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



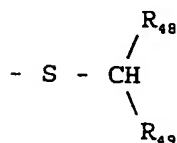
 wherein R_{45} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, 25 aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl,

heterocyclylalkyl, cycloalkylalkenyl,
 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
 heterocyclylalkenyl, alkylthioalkyl,
 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
 5 heteroarylthioalkyl, heterocyclylthioalkyl,
 alkylthioalkenyl, alkenylthioalkenyl,
 alkynylthioalkenyl, arylthioalkenyl,
 heteroarylthioalkenyl, heterocyclylthioalkenyl,
 aminocarbonylalkyl, aminocarbonylalkenyl,
 10 aminocarbonylalkynyl, aminocarbonylaryl,
 aminocarbonylheteroaryl, and
 aminocarbonylheterocyclyl,
 -SR₄₆, and -CH₂R₄₇,

wherein R₄₆ is selected from the group
 15 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl, and

R₄₇ is selected from the group consisting of
 hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl
 and heterocyclyl; and

20

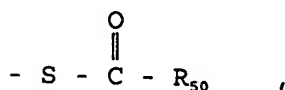


25

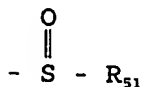
wherein R₄₈ is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 alkynyl, aryl, heteroaryl and heterocyclyl, and

R₄₉ is selected from the group consisting of
 alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy,
 30 heterocycliloxy, haloalkyl, haloalkenyl,
 haloalkynyl, haloaryl, haloheteroaryl and
 haloheterocyclyl;

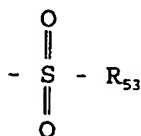
35



wherein R_{50} is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy,
 alkenoxy, alkynoxy, aryloxy, heteroaryloxy and
 heterocyclyloxy;



wherein R_{51} is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl, heterocyclyl, haloalkyl, haloalkenyl,
 haloalkynyl, haloaryl, haloheteroaryl and
 haloheterocyclyl; and



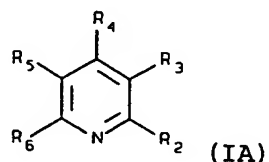
wherein R_{53} is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_5 is selected from the group
 consisting of heterocyclylalkyl and heterocyclylalkenyl,
 then the heterocyclyl radical of the corresponding
 heterocyclylalkyl or heterocyclylalkenyl is other than a
 δ -lactone; and

provided that when R_4 is aryl, heteroaryl or
 heterocyclyl, and one of R_2 and R_6 is trifluoromethyl,
 then the other of R_2 and R_6 is difluoromethyl.

In another embodiment, the method comprises the administration of a therapeutically effective amount of a substituted pyridine of Formula IA:



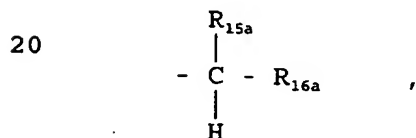
5 wherein:

R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and
 10 alkoxy carbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,

15 $-CO_2R_7$,

wherein R_7 is selected from the group consisting of hydrogen, alkyl (preferably methyl or ethyl) and cyanoalkyl; and



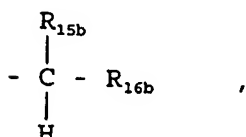
wherein R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, and

25 R_{16a} is selected from the group consisting of alkyl, aryl and heteroaryl;

- R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, alkylamino, trialkylsilyl,
- 5 -OC(O)N(R_8)₂, wherein R_8 is aryl,
 -SO₂ R_9 , wherein R_9 is aryl,
 10 -OP(O)(OR₁₀)₂, wherein R_{10} is alkyl, and
 -OP(S)(OR₁₁)₂, wherein R_{11} is alkyl;

- R_5 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, haloalkyl, alkynyl, heterocyclyl, heteroaryl, alkoxy, aryloxy, arylcarbonyloxyalkyl, heterocyclylalkyl, alkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, cyano, hydroxymethyl,
- 15 -CO₂ R_{14} ,
 wherein R_{14} is alkyl;

20

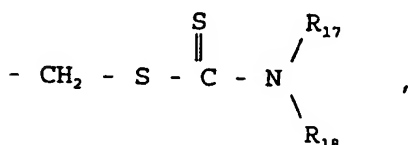


25

wherein R_{15b} is selected from the group consisting of hydroxy, hydrogen, alkylthio and alkoxy, and

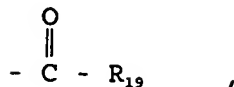
R_{16b} is selected from the group consisting of alkyl, aryl and heteroaryl;

30



41

wherein R_{17} and R_{18} are independently alkyl;



5

wherein R_{19} is selected from the group consisting of aryl, heteroaryl, $-\text{SR}_{20}$, $-\text{OR}_{21}$, and $-\text{R}_{22}\text{CO}_2\text{R}_{23}$,

wherein R_{20} is selected from the group consisting of alkyl, aryl and aminoalkyl,

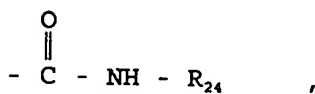
10

R_{21} is aryl,

R_{22} is alkylene, and

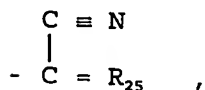
R_{23} is alkyl;

15



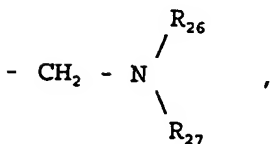
wherein R_{24} is selected from the group consisting of hydrogen, unsubstituted alkyl, and aralkyl;

20



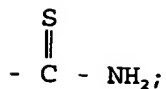
wherein R_{25} is heterocyclylidenyl;

25

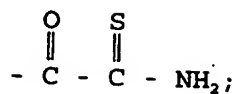


wherein R_{26} and R_{27} are independently alkyl;

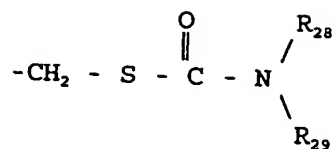
30



42



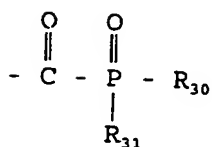
5



10

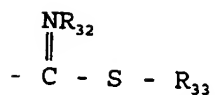
wherein R_{28} and R_{29} are independently alkyl;

15



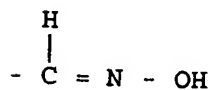
wherein R_{30} and R_{31} are independently alkoxy;

20



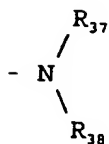
wherein R_{32} is selected from the group consisting of hydrogen and alkyl, and R_{33} is alkyl;

25



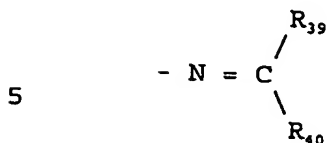
wherein R_{36} is alkyl;

30



43

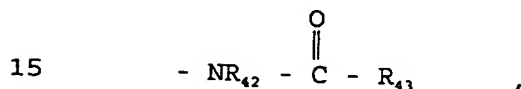
wherein R_{37} and R_{38} are independently alkyl;



wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and

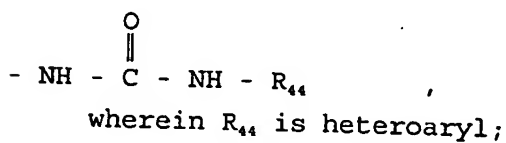
10 R_{40} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

- $N = R_{41}$, wherein R_{41} is heterocyclidenyl;



wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and

20 R_{43} is selected from the group consisting of cycloalkyl, chlorinated alkyl and substituted heteroaryl;



25 - $N = S = O$;

- $N = C = S$;

- $N = C = O$;

- N_3 ;

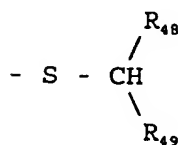
44



wherein R_{45} is selected from the group consisting of hydrogen, alkyl, haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, alkylthioalkyl, aminocarbonylalkyl, $-SR_{46}$, and $-CH_2R_{47}$,

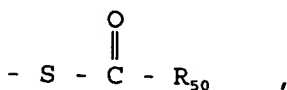
wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and

R_{47} is selected from the group consisting of aryl and heteroaryl; and

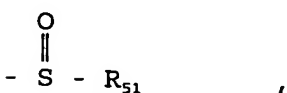


wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

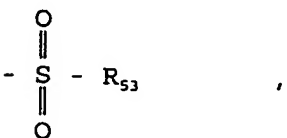
R_{49} is selected from the group consisting of alkoxy and haloalkyl;



wherein R_{50} is selected from the group consisting of alkyl, alkoxy, aryl and heteroaryl;



wherein R_{51} is selected from the group consisting of haloalkyl and alkyl; and



wherein R_{53} is aryl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_5 is selected from the group consisting of heterocyclalkyl and heterocyclalkenyl, then the heterocycl radical is other than a δ -lactone and the alkyl or alkenyl radical is other than $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}=\text{CH}-$.

Preferably, the immediately preceding embodiment involves the administration of a substituted pyridine of Formula IA as described above wherein:

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is $-\text{C}-\overset{\text{O}}{\parallel}{R_{19}}$, R_6 is trifluoromethyl, and R_{19} is the heteroaryl 1-pyrazolyl, then R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkoxy, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxy carbonyl, aryl carbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclalkylthio, alkylthioalkyl, trialkylsilyl, $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl, $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl, $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl, and $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl; and

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is the heterocycl 2-(4,5-dihydro-oxazolyl), and R_6 is trifluoromethyl, then R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxy carbonyl, aryl carbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclalkylthio,

alkylthioalkyl, alkylamino, trialkylsilyl,

-OC(O)N(R₈)₂, wherein R₈ is aryl,

-SO₂R₉, wherein R₉ is aryl,

-OP(O)(OR₁₀)₂, wherein R₁₀ is alkyl, and

5 -OP(S)(OR₁₁)₂, wherein R₁₁ is alkyl; and

when R₂ and R₆ are independently fluorinated methyl, R₃ is -CO₂R₇, R₅ is cyano, and R₇ is selected from the group consisting of hydrogen and alkyl, then R₄ is selected from the group consisting of hydrogen, hydroxy, 10 halogen, cycloalkyl, haloalkyl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, alkylamino, trialkylsilyl,

15 -OC(O)N(R₈)₂, wherein R₈ is aryl,

-SO₂R₉, wherein R₉ is aryl,

-OP(O)(OR₁₀)₂, wherein R₁₀ is alkyl, and

-OP(S)(OR₁₁)₂, wherein R₁₁ is alkyl; and

20 when R₂ is methyl, R₃ is -CO₂C₂H₅, R₅ is $\overset{\text{O}}{\parallel}\text{-C-NH-R}_{24}$, R₆ is methyl, and R₂₄ is aralkyl, then R₄ is selected from the group consisting of hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, 25 cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, alkylamino, trialkylsilyl,

-OC(O)N(R₈)₂, wherein R₈ is aryl,

30 -SO₂R₉, wherein R₉ is aryl,

-OP(O)(OR₁₀)₂, wherein R₁₀ is alkyl, and

-OP(S)(OR₁₁)₂, wherein R₁₁ is alkyl, and

when R₂ is methyl, R₃ and R₅ are -CO₂C₂H₅, and R₄ is

alkoxy, then R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl comprising at least two carbon atoms, fluorinated alkyl, chlorofluorinated alkyl, alkoxy, alkoxyalkyl, and alkoxycarbonyl,

5 when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{R}_7$, R_4 is alkenyl, R_5 is CO_2CH_3 , and R_6 is trifluoromethyl, then R_7 is selected from the group consisting of alkyl and cyanoalkyl,

10 when R_2 is methyl, R_4 is hydrogen, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is methyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms, and cyanoalkyl,

15 when R_2 is difluoromethyl, R_4 is hydrogen, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms, and cyanoalkyl,

20

 when R_2 is difluoromethyl, R_4 is alkylthioalkyl, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of alkyl and cyanoalkyl,

25

 when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_4 is alkyl, R_5 is $-\text{CO}_2\text{CH}_3$, then R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl comprising at least two carbon atoms, fluorinated alkyl, chlorofluorinated alkyl, alkoxy, alkoxyalkyl, and alkoxycarbonyl,

30

when R_2 is difluoromethyl, R_4 is alkyl, R_5 is $-\text{CO}_2R_{14}$,
 R_6 is trifluoromethyl, and R_{14} is alkyl, then R_3 is
selected from the group consisting of hydroxy and $-\text{CO}_2R_7$,
wherein R_7 is selected from the group consisting of
5 hydrogen, alkyl and cyanoalkyl,

when R_2 is selected from the group consisting of
hydroxy and trifluoromethyl, R_4 and R_5 are hydrogen, and
 R_6 is selected from the group consisting of methyl and
trifluoromethyl, then R_3 is selected from the group
10 consisting of hydroxy, amido and $-\text{CO}_2R_7$, wherein R_7 is
selected from the group consisting of alkyl and
cyanoalkyl,

when R_2 is selected from the group consisting of
methyl, difluoromethyl and trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$,
15 R_5 is hydrogen, and R_6 is selected from the group
consisting of methyl and trifluoromethyl, then R_4 is
selected from the group consisting of hydrogen, hydroxy,
halogen, cycloalkyl, alkenyl, aryl, heteroaryl,
cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy,
20 aralkoxy, alkoxy carbonyl, thio, alkylthio, arylthio,
cycloalkylthio, heterocyclylthio, alkylthioalkyl,
alkylamino, trialkylsilyl,
 $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl,
 $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl,
25 $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl; and
 $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl; and

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is
hydroxy, and R_5 is hydrogen, then R_6 is selected from the
group consisting of hydroxy, alkyl, fluorinated alkyl,
30 alkoxy, alkoxyalkyl and alkoxy carbonyl; and

when R_2 is trifluoromethyl, R_3 is selected from the
group consisting of $-\text{CO}_2\text{H}$ and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is methyl, and R_6

is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, alkylamino, trialkylsilyl, -OC(O)N(R_8)₂, wherein R_8 is aryl, -SO₂ R_9 , wherein R_9 is aryl, -OP(O)(OR₁₀)₂, wherein R_{10} is alkyl, and -OP(S)(OR₁₁)₂, wherein R_{11} is alkyl.

In another embodiment, the method comprises the administration of a therapeutically effective amount of a substituted pyridine of Formula IA as defined in one of the embodiments discussed above wherein:

R_2 is selected from the group consisting of methyl and fluorinated methyl; and

R_3 is -CO₂ R_7 , wherein R_7 is selected from the group consisting of hydrogen, methyl and ethyl.

Pharmaceutically Acceptable Salts

Also included in the family of compounds of Formulae I, IA and IB used in the method of the present invention (as well as in the family of novel compounds of Formula IIA and IIB discussed below) are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic,

hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

Treatment of CETP-Mediated Disorders

The methods of this invention additionally can be used, for example: (i) to inhibit cholesteryl ester transfer protein (CETP) activity, (ii) to decrease the concentrations of low density lipoprotein (LDL) and/or raise the level of high density lipoprotein (HDL), or otherwise alter lipoprotein profiles, resulting in a therapeutically beneficial plasma lipid profile; (iii) for the primary and secondary treatment of coronary artery disease, myocardial infarction and agina; (iv) for the treatment of dyslipidemia (hypoalphalipoproteinaemia), hyperlipoproteinaemia (chylomicronemia and hyperapobetalipoproteinaemia), peripheral vascular disease, hypercholesterolemia,

atherosclerosis, and other CETP-mediated disorders; (v) for the prophylactic treatment of subjects who are at risk of developing CETP-mediated disorders; and (vi) to lower the risk of atherosclerosis. The methods would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

Besides being useful for human treatment, these methods are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

Without being limited to a specific theory, applicant hypothesizes that the CETP molecule contains one or more specific hydrophobic binding sites that can accommodate the substituted pyridines of the present invention. Binding of the substituted pyridine to these sites is sufficient to inhibit CETP. This binding is generally rapid and reversible.

It is additionally hypothesized that the CETP molecule contains a cysteine at or near these hydrophobic binding sites. Inhibition potency can be enhanced by selecting a substituted pyridine which is capable of undergoing a disulfide exchange with this cysteine. This disulfide exchange is time-dependent and irreversible. While inhibition potency may be enhanced as a result of this disulfide exchange, substituted pyridines which are effective inhibitors and which do not undergo the disulfide exchange may be more desirable given the generally irreversible nature of the disulfide exchange reaction.

It is further hypothesized that such disulfide-modified CETP molecules can aggregate, perhaps as a result of conformational changes induced by interaction with the substituted pyridine.

Additional Embodiments of Novel Methods

In another embodiment, the method comprises the administration of a therapeutically effective amount of a compound of Formula IA wherein:

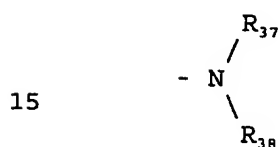
5 R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

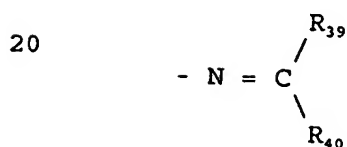
R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl;

10 R_5 is selected from the group consisting of:

heteroaryl (preferably 1-pyrrolyl);



wherein R_{37} and R_{38} are independently alkyl;

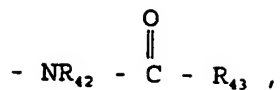


25 wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and

R_{40} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclylalkoxy, and alkylthio;

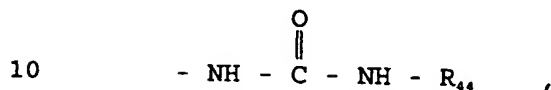
- $N = R_{41}$,

30 wherein R_{41} is heterocyclylidenyl;

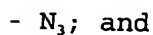
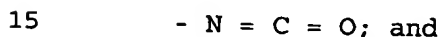
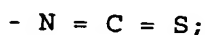
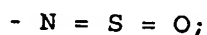


5 wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and

R_{43} is selected from the group consisting of cycloalkyl, chlorinated alkyl, and heteroaryl;



wherein R_{44} is heteroaryl (preferably substituted pyridyl);



R_6 is fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof.

20 In still another embodiment, the method comprises the administration of a therapeutically effective amount of a compound of Formula IA wherein:

R_2 is fluorinated alkyl;

25 R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of alkyl,

haloalkyl, cycloalkyl, alkoxy and alkylthio;

R_5 is selected from the group consisting of:

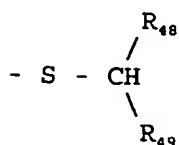
- SR_{45} ,

5 wherein R_{45} is selected from the group consisting of hydrogen, alkyl, haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, aminocarbonylalkyl, alkylthioalkyl, - SR_{46} , and - CH_2R_{47} ,

10 wherein R_{46} is selected from the group consisting of aryl (preferably substituted aryl) and heteroaryl (preferably substituted pyridyl), and

R_{47} is selected from the group consisting of aryl and heteroaryl (R_{47} is preferably substituted aryl); and

15

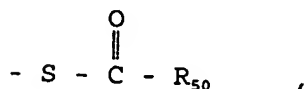


20

wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

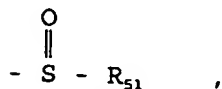
R_{49} is selected from the group consisting of alkoxy and haloalkyl;

25



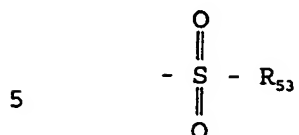
wherein R_{50} is selected from the group consisting of alkyl, alkoxy, aryl and heteroaryl (preferably substituted heteroaryl);

30



wherein R_{51} is selected from the group

consisting of alkyl and haloalkyl; and



wherein R_{53} is aryl; and

R_6 is fluorinated alkyl;

10 or a pharmaceutically acceptable salt or tautomer thereof.

In still another embodiment, the method comprises the administration of a therapeutically effective amount of a compound of Formula IA wherein:

15 R_2 is selected from the group consisting of alkyl and fluorinated alkyl;

R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

20 R_4 is selected from the group consisting of hydroxy, alkoxy, aralkoxy, alkoxycarbonyl, alkylthio, arylthio, $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl, $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl, $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl, and $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl;

25 R_5 is selected from the group consisting of hydrogen, hydroxy, halogen, alkoxy, and aryloxy; and

R_6 is selected from the group consisting of hydrogen, fluorinated alkyl and alkoxycarbonyl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydroxy and R_5 is hydrogen, then R_6 is selected from the group consisting of fluorinated alkyl and alkoxycarbonyl.

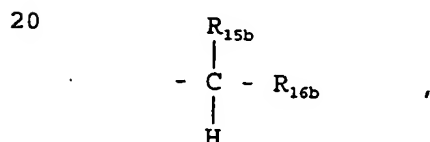
In yet another preferred embodiment, the method comprises the administration of a therapeutically effective amount of a compound of Formula IA wherein:

R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen, alkyl and cyanoalkyl;

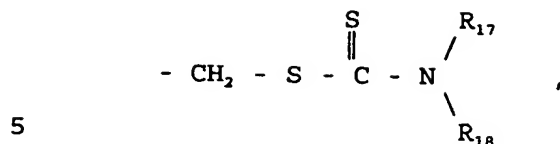
R_4 is selected from the group consisting of alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, arylcarbonyloxy, arylthio, and alkylamino;

R_5 is selected from the group consisting of alkyl, haloalkyl, alkynyl, heterocyclyl, heteroaryl, heterocyclylalkyl, arylcarbonyloxyalkyl, alkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, cyano,

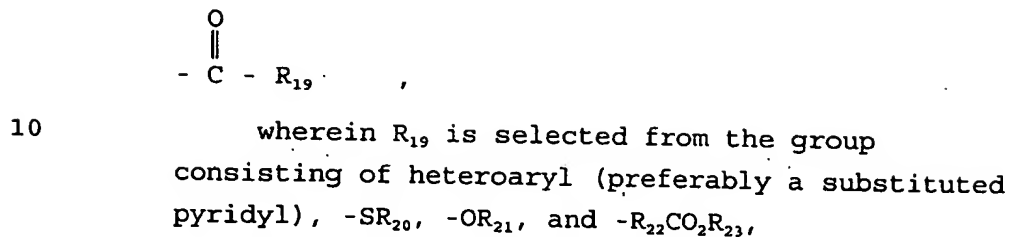


wherein R_{15a} is selected from the group consisting of hydroxy, alkylthio and alkoxy, and R_{16b} is selected from the group consisting of alkyl and heteroaryl;

57



wherein R_{17} and R_{18} are each alkyl;



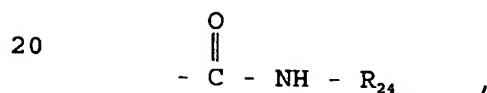
wherein R_{20} is selected from the group consisting of alkyl, aryl (preferably substituted aryl) and aminoalkyl,

15

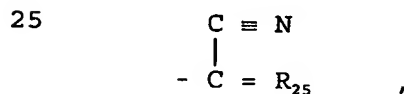
R_{21} is aryl (preferably substituted aryl),

R_{22} is alkylene, and

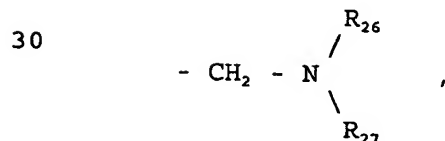
R_{23} is alkyl;



wherein R_{24} is selected from the group consisting of hydrogen, unsubstituted alkyl, and aralkyl;

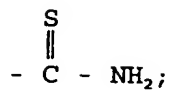


wherein R_{25} is heterocyclylidenyl;

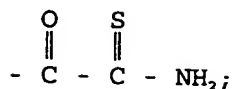


wherein R_{26} and R_{27} are independently alkyl;

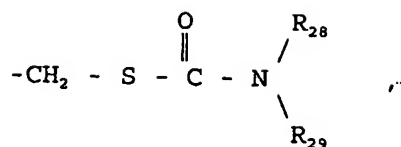
58



5

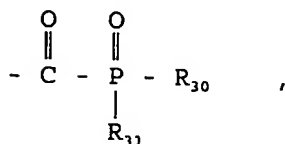


10



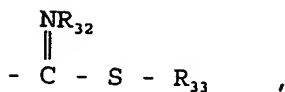
wherein R_{28} and R_{29} are independently alkyl;

15



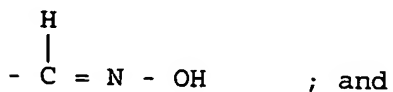
20

wherein R_{30} and R_{31} are each alkoxy;

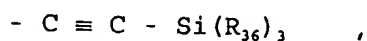


25

wherein R_{32} is selected from the group consisting of hydrogen and alkyl, and R_{33} is alkyl;



30



wherein R_{36} is alkyl; and

R_6 is selected from the group consisting of hydrogen, fluorinated alkyl and alkoxy,

R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, heteroarylalkyl, alkoxy, alkoxy carbonyl, aralkenyl, thio, alkylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, and trialkylsilyl;

R_5 is CO_2R_{14} , wherein R_{14} is alkyl;

R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, and alkoxyalkyl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that:

when R_2 is methyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is alkoxy, and R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl comprising at least two carbon atoms, fluorinated alkyl, and alkoxyalkyl;

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2R_7$, R_4 is alkenyl, R_5 is CO_2CH_3 , and R_6 is trifluoromethyl, then R_7 is alkyl;

when R_2 is methyl, R_4 is hydrogen, R_5 is CO_2R_{14} , R_6 is methyl, and R_{14} is alkyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms and cyanoalkyl;

when R_2 is difluoromethyl, R_4 is hydrogen, R_5 is CO_2R_{14} , R_6 is trifluoromethyl, and R_{14} is alkyl, then R_3 is

selected from the group consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms and cyanoalkyl;

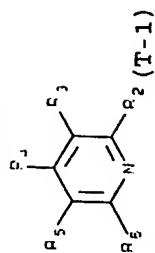
5 when R_2 is difluoromethyl, R_4 is alkylthioalkyl, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is methyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is alkyl;

10 when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_4 is alkyl, and R_5 is $-\text{CO}_2\text{CH}_3$, then R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl comprising two or more carbon atoms, fluorinated alkyl, and alkoxyalkyl; and

15 when R_2 is difluoromethyl, R_4 is alkyl, R_5 is yselected from the group consisting of $-\text{CO}_2\text{CH}_3$ and $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is selected from the group consisting of hydroxy and $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl.

20 In yet another embodiment, the method comprises the administration of a therapeutically effective amount of a compound of Formula IA which is selected from the compounds disclosed in Tables 1-8 below. While a number of the compounds disclosed in Tables 1-7 below either
25 were specifically known or generically disclosed in the art as herbicides, they were not known to possess the pharmacologic properties of the present invention. Among the compounds of Tables 1-7 used in the method which were not previously specifically known or generically
30 disclosed in the art as herbicides are those compounds identified with an asterisk.

TABLE 1



Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀
1	CF ₂ H	CO ₂ CH ₃	i-Bu	N=S=O	CF ₃	U.S. 4,885,026 EXAMPLE 165	2
2*	CF ₂ H	CO ₂ CH ₃	SH	CO ₂ C ₂ H ₅	CF ₃	EXAMPLE 2 ^A	3
3*	CF ₂ H	CO ₂ CH ₃	i-Bu	CH ₂ S-(4-t-butylphenyl)	CF ₃	EXAMPLE 3 ^A	9
4*	CF ₂ H	CO ₂ CH ₃	S-(4,5-dihydro-2-thiazolyl)	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,698,093 EXAMPLE 169	6
5*	CF ₂ H	CO ₂ CH ₃	i-Bu	SC(O)C ₁₅ H ₃₁	CF ₃	EXAMPLE 23 ^A	8
6	CF ₂ H	CO ₂ CH ₃	i-Bu	SCO ₂ CH ₃	CF ₃	EXAMPLE 11 ^A	8
7	CF ₂ H	CO ₂ CH ₃	i-Bu	SH	CF ₃	EXAMPLE 1 ^A	8.75
8	CF ₂ H	CO ₂ CH ₃	i-Bu	(1,4-dithian-2-ylidene)amino	CF ₃	U.S. 5,129,943	10
9	CF ₂ H	CO ₂ -t-Bu	i-Bu	CO ₂ -t-Bu	CF ₃	EXAMPLE 43 EXAMPLE 9 ^A	20
10	CF ₃	CO ₂ C ₂ H ₅	OC(O) [4-trifluoromethyl) - phenyl]	CH ₃	CF ₃	U.S. 4,655,816 EXAMPLE 61	25
11	CF ₃	CO ₂ C ₂ H ₅	S-(4-i-propylphenyl)	CH ₃	CF ₃	EXAMPLE 4 ^A	25

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀ (μm)
12	CF ₃	CO ₂ CH ₃	i-Bu	4,5-dihydro-2-thiazolyl	CF ₃	U.S. 4,988,384	25
13	CF ₂ H	CO ₂ CH ₃	i-Bu	CH(OH)-2-furyl	CF ₃	EXAMPLE 21	30
14	CF ₂ H	CO ₂ CH ₃	c-Bu	C(O)S-i-Pr	CF ₃	U.S. 5,260,262 EXAMPLE H	30
15	CF ₂ H	CO ₂ C ₂ H ₅	i-Bu	(tran-4,5-dichloro-4,5-dihydro-3-isoxazolyl N=C(OCH ₃)CH ₂ Br	CF ₃	EXAMPLE 12 ^A	30
16*	CF ₂ H	CO ₂ CH ₃	i-Bu	4,5-dihydro-4-ethylidene-5-oxo-2-oxazolyl N=C=S	CF ₃	U.S. 5,125,961	30
17	CF ₂ H	CO ₂ CH ₃	i-Bu	4,5-dihydro-4-ethylidene-5-oxo-2-oxazolyl N=C=S	CF ₃	EX.37, CMPD. 24 U.S. 4,885,026 SEE EX. 131	30
18	CF ₂ H	CO ₂ CH ₃	i-Bu	4,5-dihydro-4-ethylidene-5-oxo-2-oxazolyl N=C=S	CF ₃	U.S. 4,988,384	30
19*	CF ₂ H	CO ₂ CH ₃	i-Bu	C≡CSi(CH ₃) ₃	CF ₃	EXAMPLE 73	35
20	CH ₃	CO ₂ C ₂ H ₅	i-Bu	CO ₂ C ₂ H ₅	CF ₃	U.S. 5,129,943 EX. 41, STEP A	35
21	CF ₂ H	CO ₂ CH ₃	CH ₃ C-Pr	CH(CH ₃)SC ₂ H ₅	CF ₃	EXAMPLE 21 ^A	37.5
22	CF ₂ H	CO ₂ C ₂ H ₅	S-C-C ₅ H ₉	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 246	40
23	CF ₃	CO ₂ C ₂ H ₅	S-Ph	H	CF ₃	U.S. 5,169,432 EXAMPLE 56	40
24	CF ₃	CO ₂ CH ₃	OP(S)(OCH ₃) ₂	H	CF ₃	U.S. 4,698,093 EXAMPLE 109	40
25*	CF ₃	CO ₂ CH ₃	OC(O)NPh ₂	H	CF ₃	U.S. 4,655,816 EXAMPLE 23	40
26	CF ₂ H	CO ₂ CH ₃	i-Bu	CH ₃ SC ₂ H ₅	CF ₃	U.S. 4,655,816 EXAMPLE 93	40
27*	CF ₂ H	CO ₂ CH ₃	i-Bu	N=C(OCH ₃)SCH ₃	CF ₃	EXAMPLE 13 ^A	40
						U.S. 5,169,432 EXAMPLE 47	40
						EXAMPLE 34 ^A	40

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀ (μm)
28	CF ₂ H	CO ₂ CH ₃	i-Bu	C≡CH	CF ₃	U.S. 5,125,961	40
29*	CF ₂ H	CO ₂ CH ₃	i-Bu	N=C(OCH ₃)c-Pr	CF ₃	EXAMPLE 117	40
30*	CF ₂ H	CO ₂ CH ₃	i-Bu	N=CHOCH ₃ -(2-oxiranyl)	CF ₃	U.S. 4,885,026 SEE EX. 131 EXAMPLE 36 ^A	40
31*	CF ₃	CO ₂ C ₂ H ₅	Si(CH ₃) ₃	CO ₂ C ₂ H ₅	CF ₃	EXAMPLE 26 ^A	40
32	CF ₂ H	CO ₂ CH ₃	i-Bu	CH ₂ I	CF ₃	EXAMPLE 37 ^A	45
33*	CF ₂ H	CO ₂ CH ₃	i-Bu	SCH ₂ SCH ₃	CF ₃	SEE EX. 23 ^A	45
34*	CF ₂ H	CO ₂ CH ₃	i-Bu	CH(OCH ₃)-(5-isothiazolyl)	CF ₃	EXAMPLE 38 ^A	45
35*	CF ₂ H	CO ₂ CH ₃	CH ₂ -c-Pr	C(Br)=CHOCH ₃	CF ₃	EXAMPLE 52 ^A	45
36	CF ₃	CO ₂ C ₂ H ₅	i-Bu	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 7	45
37	CF ₃	CO ₂ C ₂ H ₅	OCH ₂ Ph	H	CF ₃	U.S. 4,655,816 EXAMPLE 9	45
38	CF ₂ H	CO ₂ C ₂ H ₅	c-Hx	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 21	50
39	CF ₂ H	CO ₂ C ₂ H ₅	S-t-Bu	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,698,093 EXAMPLE 108	50
40*	CF ₂ H	CO ₂ CH ₃	i-Bu	CH(OCH ₃)-(2-thienyl)	CF ₃	SEE EX. 38 ^A	50
41*	CF ₂ H	CO ₂ CH ₃	CH ₂ -c-Pr	CH ₂ OC(O)Ph	CF ₃	EXAMPLE 39 ^A	50
42*	CF ₂ H	CO ₂ CH ₃	i-Bu	N=C(SCH ₃) ₂	CF ₃	EXAMPLE 35 ^A	50
43*	CF ₂ H	CO ₂ CH ₃	i-Bu	CH ₂ SC(S)N(CH ₃) ₂	CF ₃	EXAMPLE 52 ^A	50

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀ (μm)
44*	CF ₂ H	CO ₂ CH ₃	i-Bu	S(CH ₂) ₂ Cl	CF ₃	SEE EX. 23 ^a	50
45	CF ₂ H	CO ₂ CH ₃	i-Bu	COCH ₂ CO ₂ C ₂ H ₅	CF ₃	U.S. 5,260,262	50
46	CF ₂ H	CO ₂ CH ₃	i-Bu	[3-methyl-dihydro 2(3H)-	CF ₃	SEE EX. 25	50
47	CF ₂ H	CO ₂ CH ₃	CH=C(CH ₃)Ph	thienylidene] amino	CF ₃	EXAMPLE 64	50
48*	CF ₃	CO ₂ C ₂ H ₅	Et	CO ₂ CH ₃	CF ₃ H	CMPD. 3f ^b	50
				NHC(O)NH-[2- (difluoromethyl)- 4-ethyl-5- carbethoxy-6- (trifluoromethyl)- 3-)pyridyl]		EXAMPLE 27 ^a	50
49	CF ₂ H	CO ₂ CH ₃	CH ₂ -i-Bu	CO ₂ CH ₃	CF ₃	U.S. 4,692,184	50
50	CF ₂ H	CO ₂ CH ₃	i-Bu	1,3-dithian-2-yl	CF ₃	SEE EX. 14	50
51	CF ₃	CO ₂ C ₂ H ₅	SO ₂ Ph	H	CF ₃	U.S. 4,988,384	50
52	CF ₃	CO ₂ CH ₃	OC ₂ H ₅	CO ₂ C ₂ H ₅	CF ₃	EXAMPLE 20	50
53	CF ₃	CO ₂ C ₂ H ₅	O-i-Pr	CH ₃	CF ₃	EXAMPLE 24	50
54*	CF ₃	CO ₂ CH ₃	O-i-Pr	C(O)-[2-(trifluoro- methyl)-3-carbo- methoxy-4-i- propoxy-5-pyridyl]	CF ₃	U.S. 4,698,093	50
				C(CN)=[2-(1,3- dioxolanyl)] CH ₂ N(CH ₃) ₂	H	EXAMPLE 17	50
55	CF ₂ H	CO ₂ CH ₃	CH ₂ -C-Pr	5-methyl-3- isothiazolyl C(SCH ₃)=N-i-Pr	CF ₃	U.S. 4,655,816	50
56	CF ₂ H	CO ₂ CH ₃	i-Bu		CF ₃	EXAMPLE 37	50
57	CF ₂ H	CO ₂ CH ₃	i-Bu		CF ₃	EXAMPLE 28 ^a	50
58	CF ₂ H	CO ₂ CH ₃	i-Bu		CF ₃	U.S. 5,156,670	55
						EXAMPLE 6	50
						U.S. 5,169,432	50
						EXAMPLE 50	50
						U.S. 5,125,961	50
						EXAMPLE 17	55
						EXAMPLE 40 ^a	55

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀ (μm)
59	CF ₃ H	CO ₂ CH ₃	i-Bu	1,3-dioxan-2-yl	CF ₃	U.S. 4,988,384 EXAMPLE 109	55
60	CF ₃ H	CO ₂ CH ₃	CH ₂ -c-Pr	CH ₂ SCH ₃	CF ₃	U.S. 5,169,432 EXAMPLE 47	60
61	CF ₃ H	CO ₂ CH ₃	i-Bu	1,3-dithiolan-2-yl	CF ₃	U.S. 4,988,384 EXAMPLE 19	60
62	CF ₃ H	CO ₂ CH ₃	Pr	C(O)SC ₂ H ₅	CF ₃	U.S. 4,692,184 SEE EX. 140	60
63	CF ₃ H	CO ₂ CH ₃	S-i-Pr	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,698,093 EXAMPLE 32	60
64	CF ₃	CO ₂ C ₂ H ₅	OC ₂ H ₅	CN	CF ₃	U.S. 4,698,093 EXAMPLE 25	60
65	CF ₃	CO ₂ C ₂ H ₅	OC ₂ H ₅	CN	OC ₂ H ₅	U.S. 4,609,399 EXAMPLE 24	60
66	CF ₃ H	CO ₂ CH ₃	c-Bu	SC ₂ H ₅	CF ₃	U.S. 4,789,395 EXAMPLE 76	60
67	CF ₃ H	CO ₂ CH ₃	CH ₂ -[2-(methylthio)-4-pyrimidinyl]	CO ₂ CH ₃	CF ₃	EXAMPLE 20 ^a	60
68	CF ₃ H	CO ₂ CH ₃	i-Pr	C(SCH ₃)=NCH ₃	CF ₃	SEE EX. 40 ^a	65
69	CF ₃ H	CO ₂ CH ₃	i-Bu	C(O)SCH ₃	CF ₃	U.S. 4,692,184 SEE EX. 140	65
70*	CF ₃ H	CO ₂ CH ₃	c-Bu	1-pyrrolyl	CF ₃	EXAMPLE 29 ^a	65
71	CF ₃ H	CO ₂ CH ₃	CH ₂ -c-Pr	N(CH ₃) ₂	CF ₃	U.S. 5,037,469 EXAMPLE 7	70
72	CF ₃	CO ₂ C ₂ H ₅	CH ₂ SCH ₃	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 SEE EX. 6	70
73	CF ₃ H	CO ₂ CH ₃	CH ₂ S-i-Pr	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 SEE EX. 162	70
74	CF ₃ H	CO ₂ CH ₃	CH=C(C ₂ H ₅) ₂	CO ₂ CH ₃	CF ₃	SEE CMPD. 3d ^b	70
75*	CF ₃	CO ₂ CH ₃	i-Bu	C(O)NHCH ₂ -(4-chlorophenyl)	CF ₃ H	U.S. 4,692,184 SEE EX. 89	70

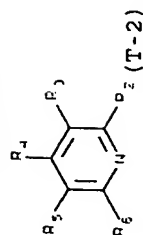
Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀ (μm)
76	CF ₃	CO ₂ C ₂ H ₅	Br	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,698,093	70
77*	CF ₃ H	CO ₂ CH ₃	i-Bu	C(O)C(S)NH ₂	CF ₃	EXAMPLE 104 EXAMPLE 30 ^A	70
78	CF ₃ H	CO ₂ CH ₃	Et	N ₃	CF ₃	U.S. 4,885,026	70
79*	CF ₃ H	CO ₂ CH ₃	i-Bu	CH ₂ SC(O)N(CH ₃) ₂	CF ₃	EXAMPLE 129 EXAMPLE 53 ^A	75
80	CF ₃ H	CO ₂ CH ₃	C(CH ₃) ₂ SCH ₃	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 170	80
81	CF ₃ H	CO ₂ CH ₃	i-Bu	C(O)-(2-chloro-5-thiazolyl) CO ₂ C ₂ H ₅	CF ₃	U.S. 5,260,262 EXAMPLE 58	80
82	CF ₃	CO ₂ C ₂ H ₅	2-thienyl	CH ₂ Cl	CF ₃	U.S. 4,692,184 EXAMPLE 5	80
83	CF ₃ H	CO ₂ CH ₃	i-Bu	SCH ₃	CF ₃	U.S. 5,169,432 EXAMPLE 3	80
84	CF ₃	CO ₂ CH ₃	SCH ₃	C(O)P(O)(OC ₂ H ₅) ₂	CF ₃	U.S. 4,789,395 EXAMPLE 42	85
85*	CF ₃ H	CO ₂ CH ₃	NH-i-Pr	CO ₂ -i-Pr	CF ₃	EXAMPLE 33 ^A	90
86	CF ₃	CO ₂ -i-Pr	Et	CH ₂ SC ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 60	90
87	CF ₃ H	CO ₂ CH ₃	CH ₂ -C-Pr	2-thiazolyl	CF ₃	U.S. 5,169,432 EXAMPLE 51	90
88	CF ₃	CO ₂ CH ₃	i-Bu	CH(OH)-(2-thienyl) C(=NH)SC ₂ H ₅	CF ₃	U.S. 4,988,384 EXAMPLE 44	90
89	CF ₃ H	CO ₂ CH ₃	i-Bu		CF ₃	U.S. 5,260,262 SEE EX. H	100
90	CF ₃ H	CO ₂ CH ₃	i-Bu	CO ₂ CH ₃	CF ₃	SEE EX. 46 ^A	100
91	CF ₃ H	CO ₂ CH ₃	CH ₂ I		CF ₃	U.S. 4,692,184 EXAMPLE 132	100

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	IC ₅₀ (μm)
92*	CH ₂ OCH ₃	CO ₂ CH ₃	Pr	CO ₂ CH ₃	CH ₂ OCH ₃	EXAMPLE 32 ^a	100
93	CF ₂ H	CO ₂ CH ₃	i-Bu	5-methoxy-2-oxazolyl	CF ₃	U.S. 4,988,384	100
94	CF ₃	CO ₂ C ₂ H ₅	SC ₂ H ₅	H	CF ₃	EXAMPLE 33	100
95	CF ₂ H	CO ₂ CH ₃	CH(i-Pr)	CO ₂ CH ₃	CF ₃	U.S. 4,655,816	100
96	CH ₃	OH	CO ₂ CH ₃ CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	CH ₃	EXAMPLE 25 CMPD. 7b ^b	100
						CHEM. PHARM. BUL., 14, 18 (1966)	100

A: These examples correspond to the examples contained in the present application.

B: J. Heterocyclic Chem., 26, 1771 (1989).

TABLE 2



Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	% Transfer @ 100 μm ²
97	CF ₃ H	CO ₂ CH ₃	i-Bu	3-methyl-2-oxazolidinyl	CF ₃	U.S. 4,988,384	59
98	CF ₃ H	CO ₂ CH ₃	i-Pr	4,5-dihydro-2-oxazoly	CF ₃	EXAMPLE 14	63
99	CF ₃ H	CO ₂ CH ₃	i-Bu	C(O)NHBu	CF ₃	U.S. 4,988,384	66
100	CF ₃ H	CO ₂ CH ₃	i-Bu	NHC(O)CH ₂ Cl	CF ₃	U.S. 4,692,184	68
101*	CF ₃	CO ₂ C ₂ H ₅	OH	CO ₂ -i-Pr	H	SEE EX. 192	71
102	CH ₃	CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	OH	H	U.S. 5,114,465	72
103*	CF ₃ H	CO ₂ CH ₃	i-Bu	C(S)NH ₂	CF ₃	SEE EX. 4	73
104	CF ₃	CO ₂ C ₂ H ₅	3-pyridyl	CO ₂ C ₂ H ₅	CF ₃	EXAMPLE 41 ^A	74
105	CF ₃ H	CO ₂ CH ₃	i-Bu	CH(OH)-(4-methyl-2-thiazolyl)	CF ₃	BIOKIMYA, 33, 350 (1968)	74
106	CH ₃	CO ₂ CH ₃	i-Bu	CO ₂ CH ₃	CH ₃	SEE EX. 49 ^A	74
107*	CF ₃ H	CO ₂ CH ₃	CH ₃ -c-Pr	1-hydroxy-5-methyl-3-pyrrolidinyl	CF ₃	U.S. 4,692,184	75
108	CF ₃	CO ₂ C ₂ H ₅	OC ₂ H ₅	CONH ₂	CF ₃	EXAMPLE 8	76
109*	CF ₃	CO ₂ C ₂ H ₅	OH	OPh	H	U.S. 5,260,262	76
						SEE EX. H	
						SEE FOOTNOTE E	
						EXAMPLE 42 ^A	
						U.S. 4,698,093	
						EXAMPLE 20	
						EXAMPLE 43 ^A	

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	% transfer @ 100 μm ²
110	CF ₂ H	CO ₂ CH ₃	i-Bu	2-oxazolyl	CF ₃	EXAMPLE 44 ^a	76
111*	CF ₂ H	CO ₂ CH ₃	i-Bu	S(O)(CH ₂) ₂ Cl	CF ₃	EXAMPLE 45 ^a	78
112	CF ₂ H	CO ₂ CH ₃	CH ₂ -c-Pr	C(=NH)SCH ₃	CF ₃	EXAMPLE 46 ^a	78
113	CF ₃	CO ₂ C ₂ H ₅	4-pyridyl	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 9	80
114*	CF ₃	CO ₂ C ₂ H ₅	OH	OC ₂ H ₅	H	EXAMPLE 47 ^a	81
115	CF ₂ H	CO ₂ CH ₃	c-Bu	S(O)C ₂ H ₅	CF ₃	U.S. 4,789,395 EXAMPLE 74	82
116	CF ₃	CO ₂ CH ₃	OH	H	CO ₂ CH ₃	J. AGRIC. CHEM. 39, P. 1072 (1991)	82
117*	CF ₂ H	CO ₂ CH ₃	i-Bu	NHC(O)-[(2-chloro-4-(trifluoromethyl)-5-thiazolyl)]	CF ₃	EXAMPLE 48 ^a	83
118	CF ₂ H	CO ₂ CH ₃	i-Bu	(1,3-oxathiolan-2-ylidene) amino	CF ₃	U.S. 5,129,943 EXAMPLE 41	83
119*	CF ₂ H	CO ₂ CH ₃	c-Bu	C(S)NH ₂	CF ₃	EXAMPLE 49 ^a	84
120	CF ₂ H	CO ₂ CH ₃	Pr	CO ₂ CH ₃	CF ₃	U.S. 4,692,184 EXAMPLE 67	84
121*	CF ₃	CO ₂ C ₂ H ₅	O-i-Pr	H	H	EXAMPLE 41 ^a	88
122	CH ₃	CO ₂ CH ₃	Pr	CO ₂ CH ₃	CH ₃	ANN, 246, p.32 (1888)	88
123	CF ₂ H	CO ₂ CH ₃	NH-i-Pr	C(=NCH ₃)SCH ₃	CF ₃	U.S. 4,698,093 EXAMPLE 225	88
124	CF ₂ H	CO ₂ CH ₃	CH ₂ -c-Pr	5-oxazolyl	CF ₃	U.S. 4,988,384 SEE EX. 92	89
125*	CF ₃	CO ₂ C ₂ H ₅	OH	CO ₂ C ₂ H ₅	H	SEE EX. 41 ^a	89
126	CF ₃	CO ₂ H	S-(4-i-propylphenyl)	CH ₃	CF ₃	EXAMPLE 50 ^a	90

Compound	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	% Transfer @ 100 μm^2
127*	CF ₃	CO ₂ CH ₃	O-i-Pr	H	H	SEE EX. 41 ^a	90
128	OH	CO ₂ C ₂ H ₅	H	CO ₂ C ₂ H ₅	OH	SEE FOOTNOTE F	92
129	CF ₃	CO ₂ CH ₃	OP(O) (OC ₂ H ₅) ₂	H	CF ₃	U.S. 4,655,816 EXAMPLE 18	92
130	CH ₃	CO ₂ C ₂ H ₅	CO ₂ C ₂ H ₅	OH	H HCl salt	BIOKHIMYA, 33, 350 (1968)	94
131	CF ₂ H	CO ₂ CH ₃	i-Bu	CH(OH)-(3,5- dimethyl-4- isoxazolyl)	CF ₃	U.S. 5,260,262 SEE EX. H	93
132	CH ₃	CO ₂ CH ₃	H	CO ₂ CH ₃	CH ₃	ANN, 241, P.1 (1882)	94
133	CF ₂ H	CO ₂ CH ₃	i-Bu	CH(OH)-(2- thiazolyl) C(O)S(CH ₃) ₂ NH ₂	CF ₃	U.S. 5,260,262 SEE EX. H	95
134*	CF ₂ H	CO ₂ CH ₃	i-Bu		CF ₃	EXAMPLE 51 ^a	96
135	CF ₃	CO ₂ C ₂ H ₅	OCH ₃	Br	CF ₃	U.S. 4,885,026 EXAMPLE 140	97
136*	CF ₃	CO ₂ C ₂ H ₅	H	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 SEE EX. 1	97
137	CF ₂ H	CONH ₂	Et	CO ₂ C ₂ H ₅	CF ₃	U.S. 4,692,184 EXAMPLE 88	98
138	CF ₃	CO ₂ CH ₃	O-i-Pr	S(O) ₂ Ph	CF ₃	U.S. 4,789,395 EXAMPLE 47	98
139	CF ₂ H	CO ₂ CH ₂ CN	i-Bu	3,4-dihydro-2 thiazolyl CH=NOH	CF ₃	U.S. 4,988,384 EXAMPLE 88	98
140	CF ₂ H	CO ₂ CH ₃	i-Bu		CF ₃	U.S. 5,125,961 EXAMPLE C	99
141	CF ₂ H	CO ₂ CH ₃	i-Bu	4,5-dihydro-1H-2- imidazolyl N(CH ₃)C(O)- C-Pr	CF ₃	U.S. 4,988,384 EXAMPLE 12	99
142	CF ₂ H	CO ₂ CH ₃	i-Bu		CF ₃	U.S. 5,037,469 EXAMPLE J1	99.5
143	CF ₃	CO ₂ CH ₃	OH	H	CF ₃	U.S. 4,655,816 EXAMPLE 4	99.7

CP	R ₂	R ₃	R ₄	R ₅	R ₆	Procedure Reference	% Transfer @ 100 μm ^c
144	CF ₂ H	CO ₂ CH ₃	i-Bu	CONH ₂	CF ₃	RES. DISCL., 295, 867 (1988)	94
145*	CF ₂ H	CO ₂ CH ₃	i-Bu	SCH ₂ C(O)NH ₂	CF ₃	EXAMPLE 23 ^A	64
146*	CF ₂ H	CO ₂ CH ₃	i-Bu	SCH(CH ₃)OC ₂ H ₅	CF ₃	EXAMPLE 23 ^A	67 ^D
147*	CF ₂ H	CO ₂ CH ₃	i-Bu	SCH(CH ₃)OCH ₃	CF ₃	EXAMPLE 23 ^A	15 ^D
148*	CF ₂ H	CO ₂ CH ₃	i-Bu	S(CH ₃) ₂ F	CF ₃	EXAMPLE 2 ^A	32 ^D
149*	CF ₂ H	CO ₂ CH ₃	i-Bu	SC(O)CH ₃	CF ₃	SEE EX. 23 ^A	31 ^D
150*	CF ₂ H	CO ₂ CH ₃	i-Bu	S-(tetrahydro-2-furyl)	CF ₃	EXAMPLE 31 ^A	95 ^D

A: These examples correspond to the examples contained in the present application.

B: J. Heterocyclic Chem., 26, 1771 (1989).

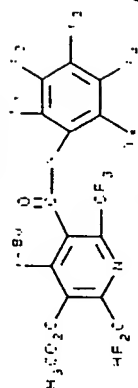
C: All compounds in Table 2 exhibited an IC₅₀ greater than or equal to 100 μm when tested.

D: % transfer at 10 μm.

E: Compound 106 is prepared according to a procedure similar to that disclosed in Ann., 246, p. 32 except using isovaleraldehyde as the reagent.

F: Compound 128 is prepared according to a procedure similar to that disclosed in Collect. Czech. Chem. Commun., 34, p. 427-441 (1969) except using ethyl cyanoacetate as the reagent instead of methyl cyanoacetate.

TABLE 3



Compound	X	Y ₁	Y ₂	Y ₃	Y ₄	Y ₅	mp (°C)	IC ₅₀ (μm)
151*	S	H	t-Bu	H	t-Bu	H	102.5-108.5	60
152*	S	Me	H	Me	H	H	98.5-102.5	60
153*	S	OMe	H	H	H	H	100-102	100
154*	S	H	OMe	H	H	H	87-88.5	100
155*	S	t-Bu	H	t-Bu	H	H	115.5-120.5	50
156*	S	H	H	t-Bu	H	H	60.5-62.5	100
157*	S	i-Pr	H	H	H	H	-	60
158*	S	H	Me	H	Me	H	96-99	100
159*	S	H	H	SMe	H	H	112-114	80
160*	S	CH ₂ -(4-fluorophenyl)	H	i-Pr	H	H	86.5-91	60
161*	S	CH ₂ -(4-fluorophenyl)	H	F	H	H	105-107	70
162*	S	H	H	Cl	H	H	94-96.5	50
163*	S	Cl	H	H	Cl	H	112.5-113.5	65
164*	S	Cl	H	H	H	Cl	109.5-112.5	50
165*	O	H	OMe	H	H	H	74-75	>100 ^A
166*	O	NO ₂	H	H	H	H	102.5-105.5	>100 ^B
167*	O	H	t-Bu	H	t-Bu	H	100-103.5	60
168*	O	t-Bu	H	t-Bu	H	H	-	60
169*	O	H	H	t-Bu	H	H	-	70
170*	O	CH ₂ -(4-fluorophenyl)	H	i-Pr	H	H	102-104	40
171*	O	CH ₂ -(4-fluorophenyl)	OMe	OMe	OMe	H	131.5-133.5	70
172*	O	OMe	H	H	H	H	73-74.5	>100 ^C
173*	O	H	H	Cl	H	H	81.5-82.5	45
174*	O	H	Me	H	Me	H	90.5-94	60
175*	O	iPr	H	H	H	H	-	>100 ^D
176*	O	Me	H	NO ₂	H	Me	96-97	100
177*	O	Me	H	Me	H	H	95-99	70

A: 89% CE transferred @ 100 μm.

B: 84% CE transferred @ 100 μm.

C: 71% CE transferred @ 100 μm.

D: 58% CE transferred @ 100 μm.

TABLE 4

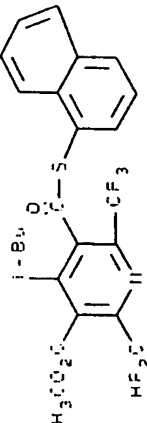
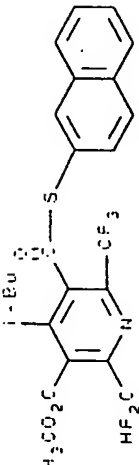
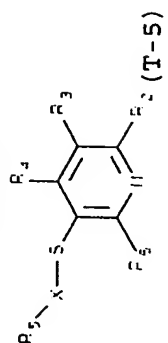
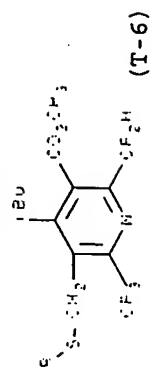
COMPOUND	Mp (°C)	IC ₅₀ (μm)	
		IC ₅₀ =70	μm
 178*	mp 125-127.5		
 179*	mp 110-115	IC ₅₀ =60	μm

TABLE 5



Compound	R_2	R_1	R_4	R_5	R_6	X	IC ₅₀
180*	CF ₂ H	CO ₂ CH ₃	i-Bu	4-t-butylphenyl	CF ₃	S	0.45
181*	CF ₂ H	CO ₂ CH ₃	i-Bu	2-(difluoromethyl)-3-carbomethoxy-4-i-butyl-6-(trifluoromethyl)-5-pyridyl	CF ₃	S	1.5
182*	CF ₂ H	CO ₂ CH ₃	i-Bu	2-(difluoromethyl)-3-carbomethoxy-4-i-butyl-6-(trifluoromethyl)-5-pyridyl	CF ₃	CH ₂	19
183*	CF ₂ H	CO ₂ CH ₃	i-Bu	2-(difluoromethyl)-3-carbomethoxy-4-i-butyl-6-(trifluoromethyl)-5-pyridyl	CF ₃	C(O)	50

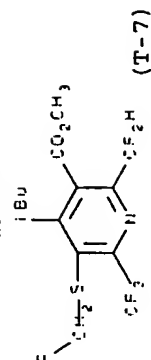
TABLE 6



Compound	R	IC ₅₀ (μm)
184*	3-bromophenyl	30
185*	4-chlorophenyl	10
186*	2,3,5,6-tetrafluorophenyl	50
187*	3,5-di-t-butylphenyl	40
188*	2-(1-methylimidazolyl)	>100 ^A
189*	5-(1-methyltetrazolyl)	>100 ^A
190*	2-(5-nitrobenzimidazolyl)	25
191*	4-(trifluoromethoxy)phenyl	10
192*	2-quinolyl	40
193*	4-bromophenyl	20
194*	pentafluorophenyl	30
195*	2,5-dichlorophenyl	50
196*	2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl	20
197*	2-(4-methylpyrimidinyl)	60
198*	4-nitrophenyl	7
199*	4-methoxyphenyl	20
200*	2-chlorophenyl	40
201*	2,6-dichlorophenyl	30
202*	8-quinolyl	80
203*	2-pyrimidinyl	70
204*	4-(acetylamino)phenyl	>100 ^B
205*	2-benzoxazolyl	20

Compound	R	IC ₅₀ (μm)
206*	4-bromo-2-(trifluoromethoxy)phenyl	50
207*	3-aminophenyl	100
208*	2-methoxyphenyl	60
209*	2-(5-methylbenzimidazolyl)	10
210*	benzimidazol-2-yl	20
211*	3-methoxyphenyl	45
212*	2-benzothiazolyl	15
213*	3-chlorophenyl	15
214*	3,4-dichlorophenyl	2
215*	2-naphthyl	2
216*	2-pyridyl	40
217*	2-bromophenyl	50
218*	[3-(carbomethoxy)-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-5-pyridyl]methyl	30
A: 90% CE transferred @ 100 μm.		
B: 80% CE transferred @ 100 μm.		

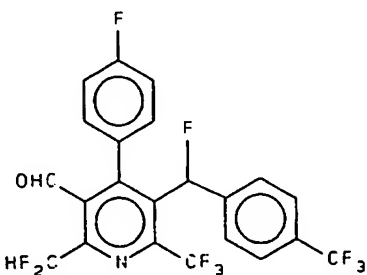
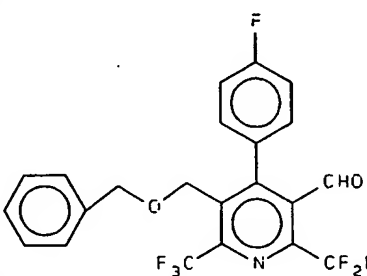
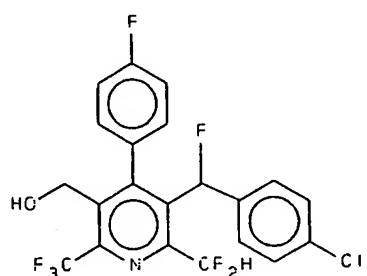
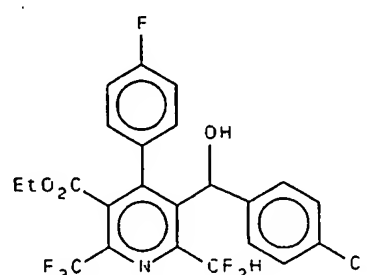
TABLE 7

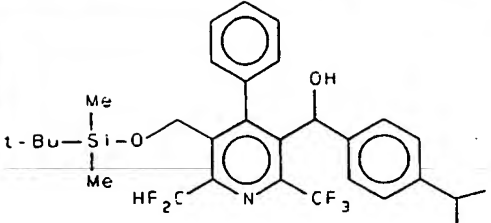
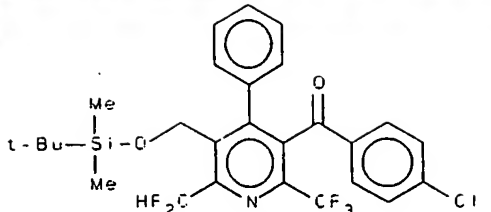
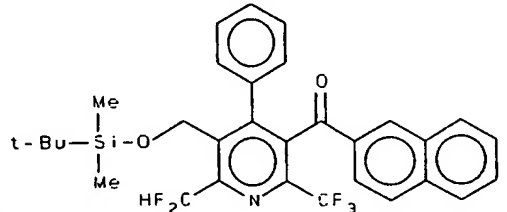
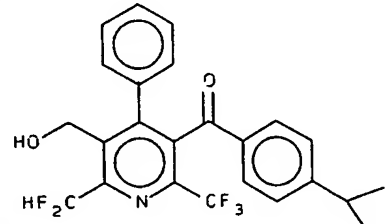
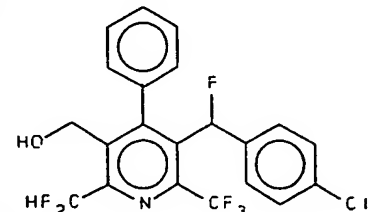


Compound	R	IC ₅₀ (μm)
219	phenyl	25
220	4-chlorophenyl	20
221	4-methoxyphenyl	40
222	3,4-dibenzoyloxyphenyl	15
223	2-nitrophenyl	50
224	4-benzoyloxyphenyl	25
225	4-biphenyl	10
226*	2-chloro-3,4-methylenedioxyphenyl	60
227	9-anthryl	30
228	3,5-bis(trifluoromethyl)phenyl	50
229	3-bromophenyl	50
230	3-nitrophenyl	50
231	3-methoxyphenyl	50
232	4-t-butylphenyl	35
233*	2-pyridyl	60
234	2,4-bis(trifluoromethyl)phenyl	20
235	4-(trifluoromethoxy)phenyl	30
236	3,4-dichlorophenyl	40
237	2,4-dichlorophenyl	30
238	1-naphthyl	45
239	2-bromophenyl	45
240	2,6-dichlorophenyl	50
241*	2-quinoliny	50
242	3-phenoxyphenyl	20
243	3,5-dichlorophenyl	50
244	pentafluorophenyl	50
245*	1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl	30
246*	8-(6-chloro-1,3-benzodioxanyl)	30

TABLE 8

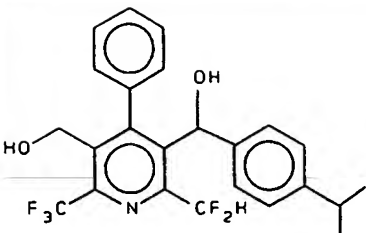
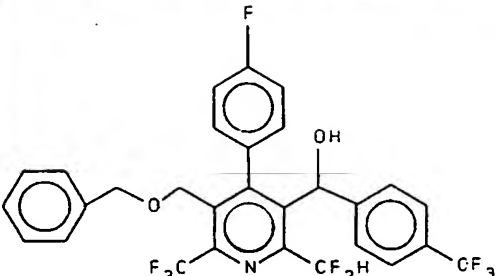
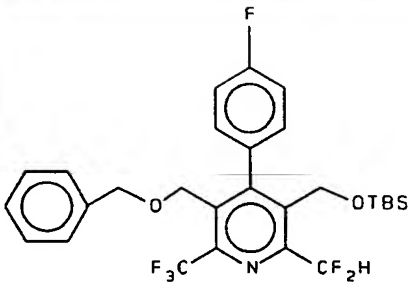
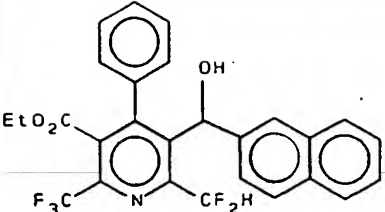
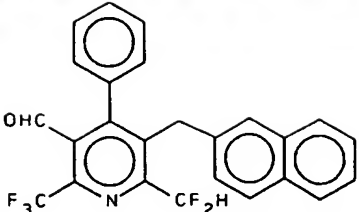
Compound Number	Structure	IC ₅₀ (μM)
247	 <chem>COc1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1C(F)c2cc(C(F)(F)F)cc(F)c2</chem>	5
248	 <chem>COc1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1C(F)c2cc(C(F)(F)F)cc(F)c2</chem>	77
249	 <chem>COc1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1C(F)c2cc(C(F)(F)F)cc(F)c2</chem>	5
250	 <chem>CCOC(=O)c1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1C(F)c2cc(Cl)cc(F)c2</chem>	40

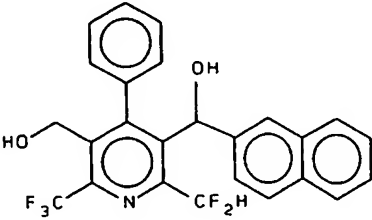
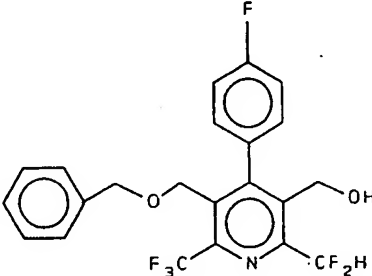
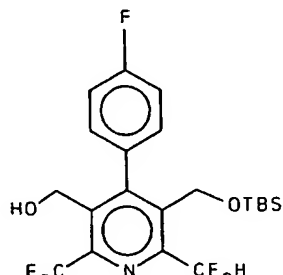
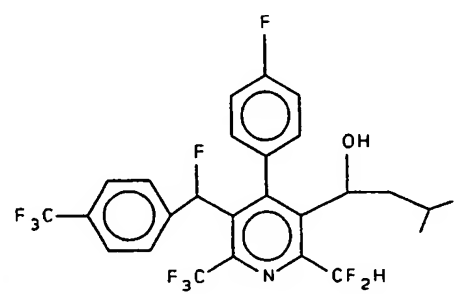
Compound Number	Structure	IC ₅₀ (μM)
251		7
252		4.5
253		19
254		55

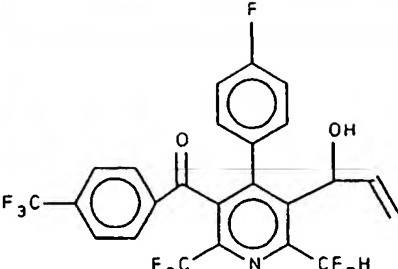
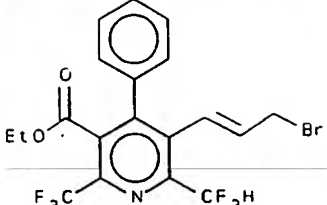
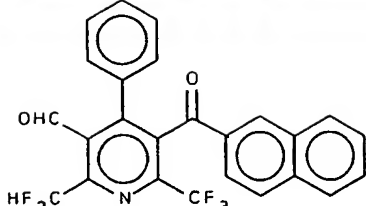
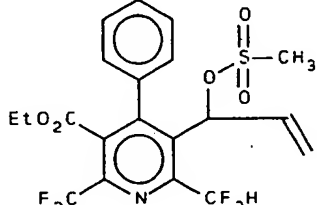
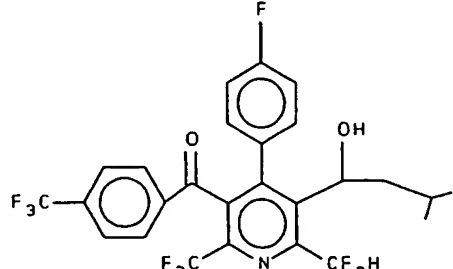
Compound Number	Structure	IC ₅₀ (μM)
260		
261		
262		
263		40
264		30

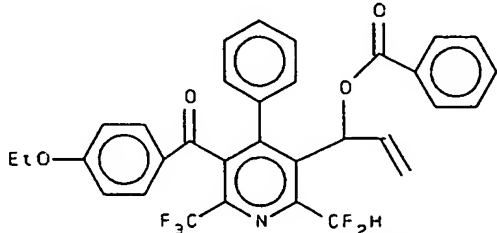
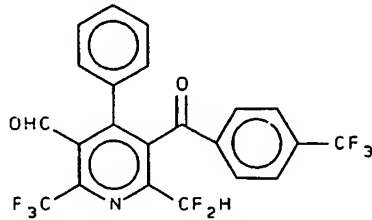
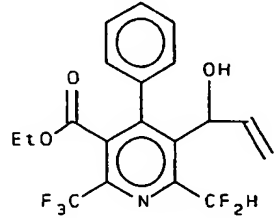
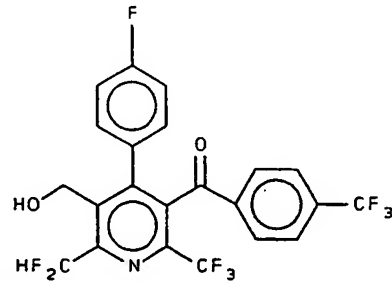
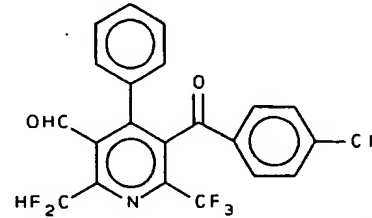
Compound Number	Structure	IC ₅₀ (μM)
265	 <chem>CC(C)c1ccc(cc1C(F)C2=CC=CC=C2)C(F)C3=CC=C(C=C3)c4cc(C(F)(F)F)c(CO)c(C5=CC=CC=C5)n4C(F)(F)F</chem>	60
266	 <chem>CC(C)c1ccc(cc1C(O)C2=CC=CC=C2)C3=CC=C(C=C3)c4cc(C(F)(F)F)c(CO)c(C5=CC=CC=C5)n4C(F)(F)F</chem>	>100
267	 <chem>CCOC(=O)c1cc(C(F)C2=CC=C(C=C2)C(F)c3cc(Cl)ccc3)c(C(F)(F)F)c(C(F)(F)F)n1C(F)(F)F</chem>	70
268	 <chem>CCOC(=O)c1cc(C(F)c2ccccc2)c(C(F)(F)F)c(C(F)(F)F)n1C(F)(F)F</chem>	70
269	 <chem>Clc1ccc(cc1C(O)C2=CC=CC=C2)C(F)C3=CC=C(C=C3)c4cc(C(F)(F)F)c(CO)c(C5=CC=CC=C5)n4C(F)(F)F</chem>	>100

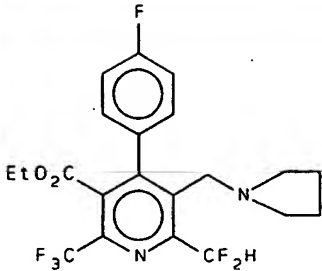
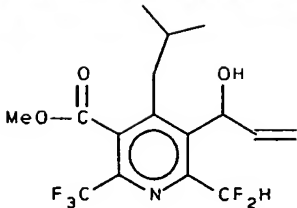
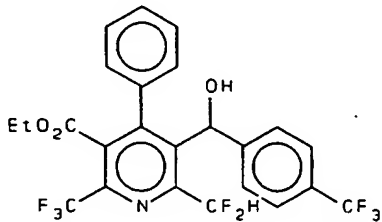
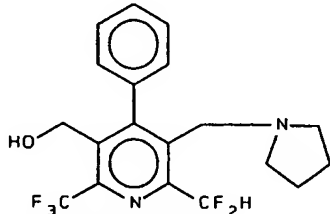
Compound Number	Structure	IC ₅₀ (μM)
270	 <chem>COc1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1Cc2ccc3ccccc3c2</chem>	>100
271	 <chem>CCOC(=O)c1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1Cc2ccc(C)cc2F</chem>	70
272	 <chem>CCOC(=O)c1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1Cc2ccc(Cl)cc2O</chem>	90
273	 <chem>CCOC(=O)c1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1Cc2ccc(C)cc2O</chem>	100
274	 <chem>CCOC(=O)c1cc(C(F)(F)F)c(C(F)(F)F)c(C(F)(F)F)c1Cc2ccc(C)cc2O</chem>	8

Compound Number	Structure	IC ₅₀ (μM)
275		>100
276		>100
277		
278		80
279		15

Compound Number	Structure	IC ₅₀ (μM)
280		>100
281		>100
282		
283		38.7

Compound Number	Structure	IC ₅₀ (μM)
284		22.7
285		
286		11.7
287		
288		19

Compound Number	Structure	IC ₅₀ (μM)
289		55.3
290		12.2
291		
292		16.2
293		10.2

Compound Number	Structure	IC ₅₀ (μM)
294		40
295		>100
296		>100
297		>100

In yet another embodiment, the method comprises the administration of a therapeutically effective amount of the compound of Formula IA wherein:

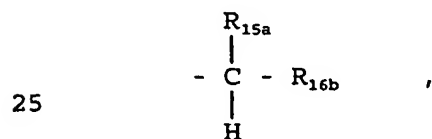
5 R_2 is selected from the group consisting of alkyl and fluorinated alkyl;

R_3 is selected from the group consisting of $-CO_2R_7$,
wherein R_7 is selected from the group consisting of
10 hydrogen and alkyl;

R_4 is selected from the group consisting of alkyl, cycloalkyl, arylcarbonyloxy, thio, arylthio, and heterocyclylthio,
15

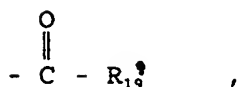
R_5 is selected from the group consisting of alkyl, heterocyclyl, arylthioalkyl, heteroarylthioalkyl,

$-CO_2R_{14}$,
20 wherein R_{14} is alkyl;

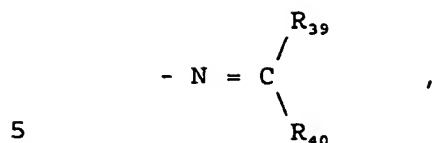


wherein R_{15b} is hydroxy, and
 R_{16b} is heteroaryl;

30



35 wherein R_{19} is $-SR_{20}$, and R_{20} is alkyl;



wherein R_{39} is alkoxy, and
 R_{40} is haloalkyl;

10 $- N = R_{41}$,
 wherein R_{41} is heterocyclylidenyl;

$- N = S = O$;

15 $- SR_{45}$,
 wherein R_{45} is selected from the group
 consisting of hydrogen, $-SR_{46}$, and $-CH_2R_{47}$,

20 wherein R_{46} is selected from the group
 consisting of aryl and heteroaryl, and
 R_{47} is selected from the group consisting of
 aryl and heteroaryl; and

25
$$- S - \overset{\overset{O}{\parallel}}{C} - R_{50} ,$$

 wherein R_{50} is selected from the group
 consisting of alkyl and alkoxy;

30 R_6 is selected from the group consisting of alkyl and
 fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer
 thereof;

35 provided that:

when R_2 is trifluoromethyl, R_3 is CO_2CH_3 , R_4 is
 isobutyl, and R_5 is $-CO_2CH_3$, then R_6 is selected from the

group consisting of alkyl comprising at least two carbon atoms and fluorinated alkyl.

In yet another embodiment, the method comprises the administration of a therapeutically effective amount of the compound of Formula IA which is selected from the compounds disclosed below:

Methyl 5-[(4-t-Butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 180);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 5);

Methyl 2-(Difluoromethyl)-5-(methoxycarbonylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 6);

Diethyl 2,6-Bis(trifluoromethyl)-4-(trimethylsilyl)-3,5-pyridinedicarboxylate (Compound 31);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(methylthiomethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 33);

Methyl 5-(1-Bromo-2-methoxyethenyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 35);

Methyl 5-(Chloroethylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 44);

Methyl 4-(i-Propoxy)-5-{[3-(methoxycarbonyl)-4-(i-propoxy)-6-(trifluoromethyl)-5-pyridyl]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 54);

5 Methyl 2-(Difluoromethyl)-4-cyclobutyl-5-(1-pyrrolyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 70);

10 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(aminothionocarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 77);

15 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[[(dimethylamino) carbonyl]thiomethyl]-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 79);

Methyl 2-(Difluoromethyl)-5-[(diethylphosphono) carbonyl]-4-(i-propylamino)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 85);

20

Dimethyl 2,6-Bis(methoxymethyl)-4-propyl-3,5-pyridinecarboxylate (Compound 92);

25 Methyl 5-[(Aminocarbonyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 145);

30 Methyl 2-(Difluoromethyl)-5-(1-ethoxyethylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 146);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(1-methoxyethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 147);

35

Methyl 2-(Difluoromethyl)-5-(2-fluoroethylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate (Compound 148);

5 Methyl 5-(Acetylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate (Compound 149);

10 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(2-tetrahydrofurylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 150);

15 Methyl 2-(Difluoromethyl)-5-{[(3,5-di-t-butylphenyl)thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 151);

20 Methyl 2-(Difluoromethyl)-5-{[(2,4-dimethylphenyl)thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 152);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(2-methoxyphenyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 153);

25 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(3-methoxyphenyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 154);

30 Methyl 2-(Difluoromethyl)-5-{[(2,4-di-t-butylphenyl)thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 155);

35 Methyl 5-{[(4-t-Butylphenyl)thio]carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 156);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(2-isopropylphenyl)thio]carbonyl}-6-(trifluoromethyl)-
3-pyridinecarboxylate (Compound 157);

5 Methyl 2-(Difluoromethyl)-5-{[(3,5-dimethylphenyl)
thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 158);

10 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(4-methylthiophenyl)thio]carbonyl}-6-(trifluoromethyl)-
3-pyridinecarboxylate (Compound 159);

15 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(2-(4-fluorobenzyl)-4-isopropylphenyl)thio]carbonyl}-6-
(trifluoromethyl)-3-pyridinecarboxylate (Compound 160);

20 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(2-(4-fluorobenzyl)-4-fluorophenyl)thio]carbonyl}-6-
(trifluoromethyl)-3-pyridinecarboxylate (Compound 161);

Methyl 5-{[(4-chlorophenyl)thio]carbonyl}-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 162);

25 Methyl 5-{[(2,5-Dichlorophenyl)thio]carbonyl}-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 163);

30 Methyl 5-{[(2,6-Dichlorophenyl)thio]carbonyl}-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 164);

35 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(2-naphthyl)thio]carbonyl}-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 178);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(1-naphthyl)thio]carbonyl}-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 179);

5 3-Methyl 5-(3-Methoxyphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate (Compound 165);

10 3-Methyl 5-(2-Nitrophenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate (Compound 166);

15 3-Methyl 5-(3,5-Di-t-butylphenyl) 2-(Difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-
pyridicarboxylate (Compound 167);

20 3-Methyl 5-(2,4-Di-t-butylphenyl) 2-(Difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3,5-pyridicarboxylate (Compound 168);

25 3-Methyl 5-(4-t-Butylphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate (Compound 169);

30 3-Methyl 5-[2-(4-Fluorobenzyl)-4-isopropylphenyl]
2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoro-
methyl)-3,5-pyridicarboxylate (Compound 170);

35 3-Methyl 5-[2-(4-Fluorobenzyl)-3,4,5-(trimethoxy)
phenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-
(trifluoromethyl)-3,5-pyridicarboxylate (Compound 171);

35 3-Methyl 5-(2-Methoxyphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate (Compound 172);

3-Methyl 5-(4-Chlorophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (Compound 173);

5 3-Methyl 5-(3,5-Dimethylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (Compound 174);

10 3-Methyl 5-(2-Isopropylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (Compound 175);

15 3-Methyl 5-(2,6-Dimethyl-4-nitrophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (Compound 176);

20 3-Methyl 5-(2,4-Dimethylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (Compound 177);

 Methyl 5-(4-*t*-Butylphenyl)dithio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 180);

25 Dimethyl 5,5'-Dithiobis[2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate] (Compound 181);

30 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]methylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 182);

- 5 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]carbonylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 183);
- 10 Methyl 5-[(3-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 184);
- 15 Methyl 5-[(4-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 185);
- 20 Methyl 5-[(2,3,5,6-Tetrafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 186);
- 25 Methyl 5-[(3,5-Di-t-butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 187);
- 30 Methyl 5-[(1-Methylimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 188);
- 35 Methyl 5-[(1-Methyltetrazol-5-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 189);
- 40 Methyl 5-[(5-Nitrobenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 190);
- 45 Methyl 5-[(4-(Trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 191);

Methyl 5-[(Quinolin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 192);

5 Methyl 5-[(4-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 193);

10 Methyl 5-[(Pentafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 194);

15 Methyl 5-[(2,5-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 195);

20 Methyl 5-[(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 196);

Methyl 5-[(4-Methylpyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 197);

25 Methyl 5-[(4-Nitrophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 198);

30 Methyl 5-[(4-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 199);

35 Methyl 5-[(2-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 200);

Methyl 5-[(2,6-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 201);

5 Methyl 5-[(Quinolin-8-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 202);

10 Methyl 5-[(Pyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 203);

15 Methyl 5-[(4-(Acetylamino)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 204);

20 Methyl 5-[(Benzoxazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 205);

Methyl 5-[(4-Bromo-2-(trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 206);

25 Methyl 5-[(3-Aminophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 207);

30 Methyl 5-[(2-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 208);

35 Methyl 5-[(5-Methylbenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 209);

Methyl 5-[(Benzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 210);

5 Methyl 5-[(3-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 211);

10 Methyl 5-[(Benzothiazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 212);

15 Methyl 5-[(3-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 213);

20 Methyl 5-[(3,4-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 214);

Methyl 5-[(2-Naphthyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 215);

25 Methyl 5-[(2-Pyridyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 216);

30 Methyl 5-[(2-bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 217);

35 Bis{3-(carbomethoxy)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-5-pyridyl)methyl Sulfide (Compound 218);

Methyl 5-[(2-Chloro-3,4-methylenedioxyphenyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 226);

- 5 Methyl 5-[(2-pyridyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 233);

- 10 Methyl 5-[(2-quinolinyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 241);

- 15 Methyl 5-[(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 245);

- 20 Methyl 5[(6-chloro-1,3-benzodioxan-8-yl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 246);

- 25 Diethyl 5,5'-(Carbonyldiimino)bis[6(difluoromethyl)-4-ethyl-2-(trifluoromethyl)-3-pyridinecarboxylate (Compound 48);

- Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
30 {[(dimethylamino)thiono]thiomethyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 43);

- 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

- 35 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]carbonyl}pyridine;

2- (Difluoromethyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- { [4-
(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

5 2- (Difluoromethyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- { [4-
(trifluoromethyl)phenyl]carbonyl}pyridine;

10 2- (Difluoromethyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- { [4-
(trifluoromethyl)phenyl]fluoromethyl}pyridine;

15 2- (Difluoromethyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- { [4-
(trifluoromethyl)phenyl]fluoromethyl}pyridine;

20 2- (Difluoromethyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- (2-
naphthylfluoromethyl)pyridine;

2- (Difluoromethyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- { [4-
(trifluoromethyl)phenyl]mercaptomethyl}pyridine;

25 2- (Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-
(trifluoromethyl)-3- { [4- (trifluoromethyl)phenyl]
mercaptomethyl}pyridine;

30 2- (Cyclopentyl)-5-hydroxymethyl-4- (4-fluorophenyl)-
6- (trifluoromethyl)-3- { [4- (trifluoromethyl)phenyl]
carbonyl}pyridine;

35 2- (1-Pyrrolidinyl)-5-hydroxymethyl-4- (4-
fluorophenyl)-6- (trifluoromethyl)-3- { [4-
(trifluoromethyl)phenyl]carbonyl}pyridine;

2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-fluorophenyl) -6- (trifluoromethyl) -3- { [4- (trifluoromethyl) phenyl] hydroxymethyl} pyridine; and

5 2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-fluorophenyl) -6- (trifluoromethyl) -3- { [4- (trifluoromethyl) phenyl] fluoromethyl} pyridine.

10 In yet another embodiment, the method comprises the administration of a therapeutically effective amount of the compound of Formula IA which is selected from the compounds disclosed below:

15 Methyl 5- (4-t-Butylphenyl) dithio-2- (difluoromethyl) -4- (2-methylpropyl) -6- (trifluoromethyl) -3-pyridine carboxylate;

20 Dimethyl 5,5'-Dithiobis[2- (difluoromethyl) -4- (2-methylpropyl) -6- (trifluoromethyl) -3-pyridinecarboxylate;

25 Methyl 5- [(3,4-Dichlorophenyl) thiomethyl] -2- (difluoromethyl) -4- (2-methylpropyl) -6- (trifluoromethyl) -3-pyridinecarboxylate;

30 Methyl 2- (Difluoromethyl) -5-isothiocyanato-4- (2-methylpropyl) -6- (trifluoromethyl) -3-pyridinecarboxylate;

35 Methyl 5- [(2-Naphthyl) thiomethyl] -2- (difluoromethyl) -4- (2-methylpropyl) -6- (trifluoromethyl) -3-pyridine carboxylate;

 Methyl 2- (difluoromethyl) -5-mercapto-4- (2-methylpropyl) -6- (trifluoromethyl) -3-pyridine-carboxylate;

105

5-Ethyl 3-Methyl 2-(difluoromethyl)-4-[(4,5-dihydro-2-thiazolyl)thio]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate;

5 Methyl 5-[(4-Nitrophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

10 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

15 Methyl 2-(Difluoromethyl)-5-(methoxycarbonylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

20 Methyl 5-[(4-t-Butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-[(1,4-dithian-2-ylidene)amino]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

25 Methyl 5-[(4-(Trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

30 Methyl 5-[(4-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

35 Methyl 5-[(5-Methylbenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Benzothiazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

5 Methyl 5-[(3-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

10 Methyl 5-{[3-(Carbomethoxy)-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-5-pyridyl]thiomethyl}-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-3-pyridinecarboxylate;

15 Di-t-Butyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate;

20 Methyl 5-[(4-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

25 Methyl 5-[(4-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

30 Methyl 5-[(Benzoxazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

35 Methyl 5-[(Benzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

107

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(4,5-dihydro-2-thiazoyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

- 5 Ethyl 2,6-Bis(trifluoromethyl)-5-methyl-4-[4-(trifluoromethylphenyl)carbonyloxy]-3-pyridinecarboxylate;

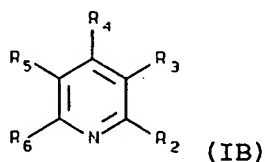
- 10 Methyl 2-(Difluoromethyl)-5-[(i-propylthio)carbonyl]-4-(cyclobutyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 4-(4-i-Propylphenylthio)-5-methyl-6-(trifluoromethyl)-3-pyridinecarboxylate;

- 15 Methyl 5-[(5-Nitrobenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate; and

- 20 In yet another embodiment, the method comprises the administration of a therapeutically effective amount of the compound of Formula IA which is Dimethyl 5,5'-dithiobis[2-difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate].

- 25 In still another embodiment, the method comprises the administration of a therapeutically effective amount of the compound of Formula IB:



- 30 wherein:

R₂ and R₆ are independently selected from the group

consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

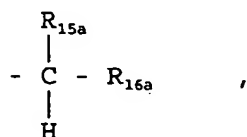
R_3 is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl

10

-CHO,

-CO₂R₇, wherein R₇ is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and

15



20

wherein R_{15a} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocycliloxy, and

25

R_{16a} is selected from the group consisting of alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aryl, heteroaryl, and heterocyclyl, arylalkoxy, trialkylsilyloxy;

30

R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy,

35

heteroaryloxy, heterocyclyloxy, alkanoyloxy, alkenoyloxy,
 alkynoyloxy, aryloxyloxy, heteroaryloxy,
 heterocyclyloxy, alkoxycarbonyl, alkenoxycarbonyl,
 alkynoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl,
 5 heterocyclyloxycarbonyl, thio, alkylthio, alkenylthio,
 alkynylthio, arylthio, heteroarylthio, heterocyclylthio,
 cycloalkylthio, cycloalkenylthio, alkylthioalkyl,
 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
 heteroarylthioalkyl, heterocyclylthioalkyl,
 10 alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,
 arylthioalkenyl, heteroarylthioalkenyl,
 heterocyclylthioalkenyl, alkylamino, alkenylamino,
 alkynylamino, arylamino, heteroarylamino,
 heterocyclylamino, aryldialkylamino, diarylamino,
 15 diheteroarylamino, alkylarylamine, alkylheteroarylamine,
 arylheteroarylamine, trialkylsilyl, trialkenylsilyl,
 triarylsilyl,

-OC(O)N(R_{8a}R_{8b}), wherein R_{8a} and R_{8b} are
 independently selected from the group consisting of
 20 alkyl, alkenyl, alkynyl, aryl, heteroaryl and
 heterocyclyl,

-SO₂R₉, wherein R₉ is selected from the group
 consisting of hydroxy, alkyl, alkenyl, alkynyl,
 aryl, heteroaryl and heterocyclyl,

25 -OP(O)(OR_{10a})(OR_{10b}), wherein R_{10a} and R_{10b} are
 independently selected from the group consisting of
 hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl, and

30 -OP(S)(OR_{11a})(OR_{11b}), wherein R_{11a} and R_{11b} are
 independently selected from the group consisting of
 alkyl, alkenyl, alkynyl, aryl, heteroaryl and
 heterocyclyl;

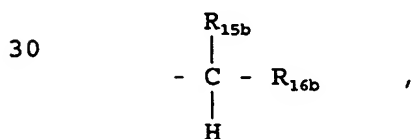
R₅ is selected from the group consisting of hydrogen,
 35 hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl,
 cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl,

heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy,
 aryloxy, heteroaryloxy, heterocyclyloxy,
 alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl,
 alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl,
 5 heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl,
 cycloalkylalkyl, cycloalkenylalkyl, aralkyl,
 heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl,
 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
 heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl,
 10 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
 heteroarylthioalkyl, heterocyclylthioalkyl,
 alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,
 arylthioalkenyl, heteroarylthioalkenyl,
 heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl,
 15 alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl,
 heterocyclyloxyalkyl, alkoxyalkenyl, alkenoxyalkenyl,
 alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl,
 heterocyclyloxyalkenyl, cyano,
 hydroxymethyl,

20

$$-\text{CO}_2\text{R}_{14},$$

25 wherein R_{14} is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl;

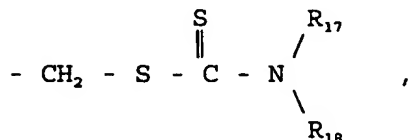


35 wherein R_{15b} is selected from the group
 consisting of hydroxy, hydrogen, halogen, alkylthio,
 alkenylthio, alkynylthio, arylthio, heteroarylthio,
 heterocyclylthio, alkoxy, alkenoxy, alkynoxy,
 aryloxy, heteroaryloxy, heterocyclyloxy, aroyloxy,
 40 and alkylsulfonyloxy, and

111

R_{16b} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkoxy, and trialkylsilyloxy;

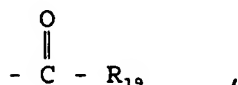
5



10

wherein R_{17} and R_{18} are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

15



20

wherein R_{19} is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-SR_{20}$, $-OR_{21}$, and $-R_{22}CO_2R_{23}$, wherein

25

R_{20} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminoaryl, aminoheteroaryl, aminoheterocyclyl, alkylheteroarylamino, arylheteroarylamino,

30

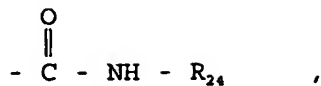
R_{21} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl,

R_{22} is selected from the group consisting of alkylene or arylene, and

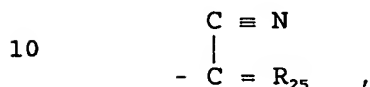
35

R_{23} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

112

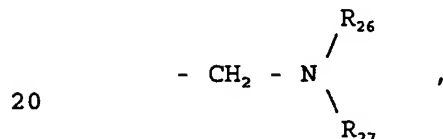


5 wherein R_{24} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, aralkenyl, and aralkynyl;



10 wherein R_{25} is heterocyclidenyl;

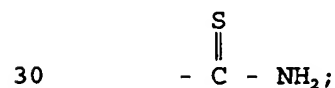
15



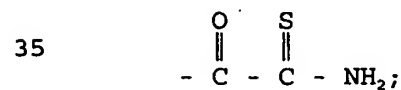
20

wherein R_{26} and R_{27} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

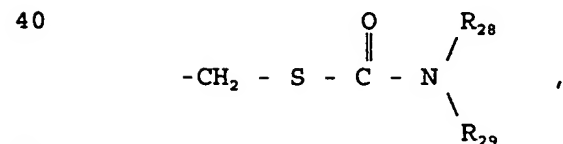
25



30



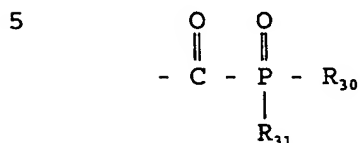
35



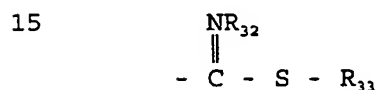
40

45 wherein R_{28} and R_{29} are independently selected

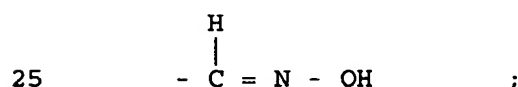
from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;



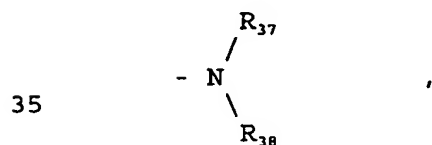
wherein R_{30} and R_{31} are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocyclxyloxy; and



wherein R_{32} and R_{33} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

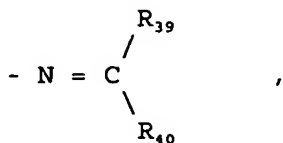


wherein R_{36} is selected from the group consisting of alkyl, alkenyl, aryl, heteroaryl and heterocyclyl;



wherein R_{37} and R_{38} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

114



5

wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyloxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio, and

10

R_{40} is selected from the group consisting of haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxy, heterocyclylalkenoxy, heterocyclylalkynoxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio;

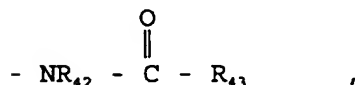
15

20



wherein R_{41} is heterocyclylidenyl;

25

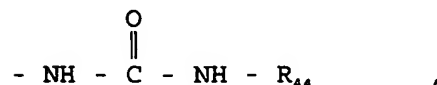


30

wherein R_{42} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl, and

R_{43} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, and haloheterocyclyl;

35



40

wherein R_{44} is selected from the group

115

consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

- N = S = O;

5

- N = C = S;

- N = C = O;

10

- N₃;

- SR₄₅ ,

15

wherein R₄₅ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, heterocyclyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkylthioalkyl, alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, aminocarbonylalkyl, aminocarbonylalkenyl, aminocarbonylalkynyl, aminocarbonylaryl, aminocarbonylheteroaryl, and aminocarbonylheterocyclyl, -SR₄₆, and -CH₂R₄₇,

20

25

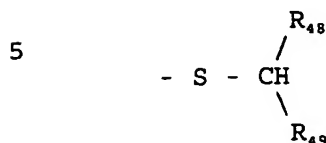
30

35

wherein R₄₆ is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

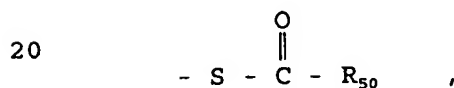
R₄₇ is selected from the group consisting of

hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl; and



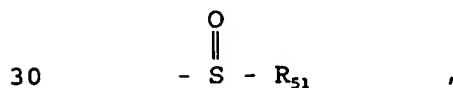
10 wherein R_{48} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and R_{49} is selected from the group consisting of alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclxyloxy, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl;

15



wherein R_{50} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclxyloxy;

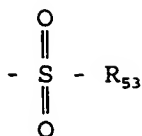
25



wherein R_{51} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and

35

117



wherein R_{53} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

10

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_5 is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, the heterocyclyl radical of the corresponding heterocyclylalkyl or heterocyclylalkenyl is other than a δ -lactone; and

20

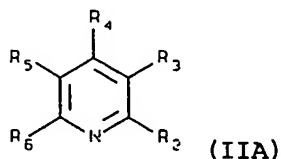
provided that when R_4 is aryl, heteroaryl or heterocyclyl, and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.

25 Novel Compounds

The present invention also relates to a class of novel substituted pyridines which are beneficial in the therapeutic and prophylactic treatment of CTEP-mediated disorders (such as coronary artery disease) as given in

30

Formula IIA:



wherein:

R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, hydroxymethyl, arylalkoxyalkyl, trialkylsilyloxyalkyl,

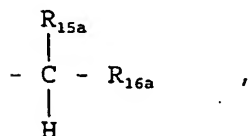
-CHO,

15

-CO₂R₇,

wherein R_7 is selected from the group consisting of hydrogen and alkyl (preferably methyl or ethyl); and

20



25

wherein R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, and

30

R_{16a} is selected from the group consisting of alkyl, haloalkyl, alkenyl, aryl and heteroaryl;

R_4 is selected from the group consisting of hydrogen, hydroxy, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, alkoxy, thio, trialkylsilyl, alkylamino, and -OC(O)N(R_8)₂, wherein R_8 is aryl;

35

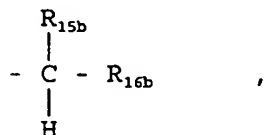
R_5 is selected from the group consisting of hydrogen,

alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl,
 haloalkynyl, aralkyl, alkoxy, aryloxy,
 cycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl,
 alkoxyalkenyl, arylcarbonyloxyalkyl, pyrrolyl,
 5 substituted pyrrolidinyl, hydroxymethyl, arylalkoxyalkyl,
 and trialkylsilyloxyalkyl,

- CO₂R₁₄,

wherein R₁₄ is alkyl;

10



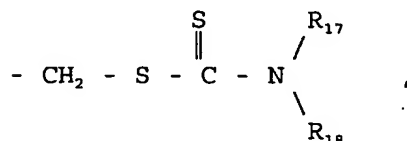
15

wherein R_{15b} is selected from the group
 consisting of hydroxy, halogen, alkoxy, and
 alkylthio, aryloxy, and alkylsulfonyloxy, and

20

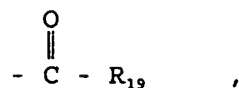
R_{16b} is selected from the group consisting of
 alkyl, alkenyl, aryl, and heteroaryl;

25



wherein R₁₇ and R₁₈ are independently alkyl;

30

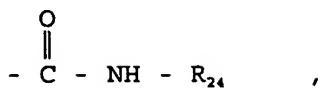


35

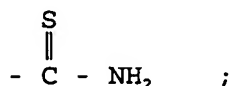
wherein R₁₉ is aryl, heteroaryl, -SR₂₀, and -OR₂₁,
 wherein R₂₀ is selected from the group
 consisting of aryl, heteroaryl and aminoalkyl, and
 R₂₁ is selected from the group consisting of
 aryl and heteroaryl;

40

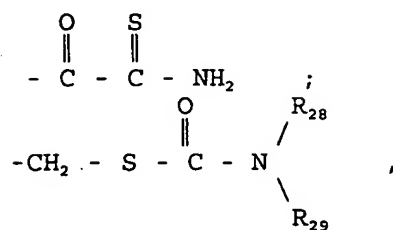
120



wherein R_{24} is aralkyl (preferably halo-
5 substituted aralkyl);



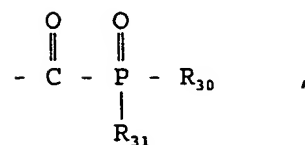
10



15

20

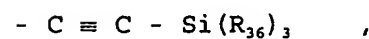
wherein R_{28} and R_{29} are independently alkyl;



25

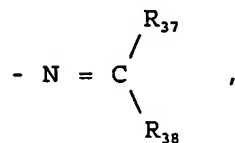
30

wherein R_{30} and R_{31} are independently alkoxy;



35

wherein R_{36} is alkyl;



40

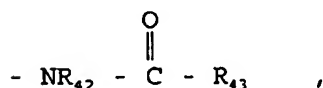
45

wherein R_{37} is selected from the group
consisting of hydrogen, alkoxy, and alkylthio, and
 R_{38} is selected from the group consisting of
haloalkyl, cycloalkyl, heterocyclalkoxy, and

alkylthio;

provided that when R_{37} is hydrogen, then R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclalkoxy;

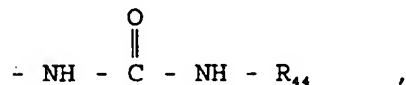
5



10

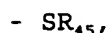
wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and R_{43} is substituted heteroaryl;

15



wherein R_{44} is selected from the group consisting of aryl and heteroaryl;

20



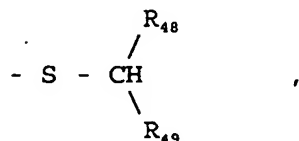
wherein R_{45} is selected from the group consisting of haloalkyl, heterocyclyl, alkylthioalkyl, aminocarbonylalkyl, $-\text{SR}_{46}$, and $-\text{CH}_2\text{R}_{47}$,

25

wherein R_{46} is selected from the group consisting of aryl (preferably substituted aryl) and heteroaryl (preferably substituted pyridyl), and

R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, tetrahydronaphthyl and benzodioxanyl;

30



35

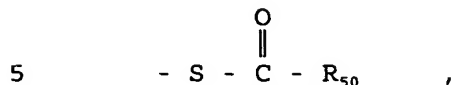
wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

40

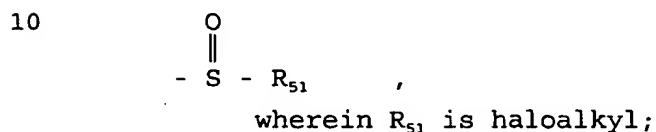
R_{49} is selected from the group consisting of

122

alkoxy and haloalkyl;



wherein R_{50} is selected from the group consisting of alkyl, alkoxy, and heteroaryl (preferably substituted heteroaryl); and



15 or a pharmaceutically acceptable salt or tautomer thereof,

provided that:

20 when R_2 is selected from the group consisting of difluoromethyl and trifluoromethyl, R_3 is selected from the group consisting of $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is hydrogen, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is selected from the
 25 group consisting of cycloalkyl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, thio, trialkylsilyl, alkylamino, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl; provided further that when R_2 , R_3 and R_5 are as defined above, and R_4 is alkoxy, then R_6 is hydrogen;

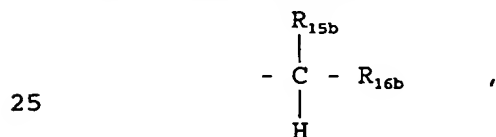
30 when R_2 is selected from the group consisting of fluorinated methyl and chlorofluorinated methyl, R_3 is selected from the group consisting of hydroxymethyl and CO_2R_7 , R_5 is selected from the group consisting of hydroxymethyl and CO_2R_{14} , R_6 is selected from the group
 35 consisting of fluorinated methyl and chlorofluorinated methyl, and R_7 and R_{14} are independently alkyl, then R_4 is

selected from the group consisting of hydrogen, thio, trialkylsilyl, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl;

when R_2 is difluoromethyl, R_3 is $-CO_2C_2H_5$, R_4 is hydrogen, R_5 is $-CO_2C_2H_5$, then R_6 is selected from the group consisting of monofluoroalkyl, difluoroalkyl and alkoxyalkyl;

when R_2 is trifluoromethyl, R_3 is $-CO_2R_7$, R_5 is methyl, R_6 is selected from the group consisting of fluorinated methyl, fluorinated ethyl and chlorofluorinated methyl, and R_7 is selected from the group consisting of hydrogen and alkyl, then R_4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl; and

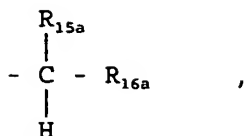
when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_3 is $-CO_2R_7$, and R_7 is alkyl, then R_5 is other than arylcarbonyl, heteroarylcarbonyl or



wherein R_{16b} is alkyl when R_{15b} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16b} is aryl or heteroaryl when R_{15b} is hydroxy;

when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_5 is $-CO_2R_{14}$, and R_{14} is alkyl, then R_3 is other than arylcarbonyl, heteroarylcarbonyl or

124



5

wherein R_{16a} is alkyl when R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16a} is aryl or heteroaryl when R_{15a} is hydroxy; and

10

when R_2 and R_6 are independently selected from fluorinated methyl and chlorofluorinated methyl, R_3 is CO_2R_7 , R_5 is hydroxy, alkoxy or aryloxy, then R_4 is selected from the group consisting of aryl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl; and

15

when R_4 is aryl and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.

20

In one embodiment, the novel compounds comprise a compound of Formula IIA as described above wherein:

R_2 is fluorinated methyl; and

25

R_3 is $-CO_2R_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl and ethyl.

30

The compounds of Formula IIA are capable of inhibiting the activity of cholesteryl ester transfer protein (CETP), and thus could be used in the manufacture of a medicament or a method for the prophylactic or therapeutic treatment of diseases mediated by CETP, such as coronary artery disease, peripheral vascular disease, hyperlipidemia, hypercholesterolemia, and other diseases attributable to either high LDL and low HDL or a combination of both. The compounds of Formula IIA would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

35

125

In another embodiment, the novel compounds comprise a compound of Formula IIA wherein:

R_2 is fluorinated alkyl;

5

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

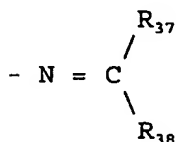
R_4 is selected from the group consisting of alkyl and cycloalkyl;

10

R_5 is selected from the group consisting of:

1-pyrrolyl;

15



20

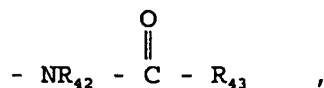
wherein R_{37} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and

R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

25

provided that when R_{37} is hydrogen, then R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclalkoxy;

30

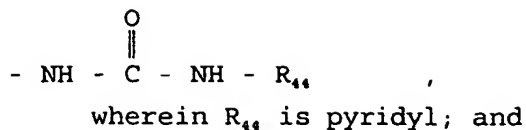


35

wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and

R_{43} is substituted heteroaryl;

126



5

R_6 is fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof.

10

In yet another embodiment, the novel compounds comprise a compound of Formula IIA wherein:

R_2 is fluorinated alkyl;

15

R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

R_4 is alkyl;

20

R_5 is selected from the group consisting of:

$-\text{SR}_{45}$

25

wherein R_{45} is selected from the group consisting of haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, alkylthioalkyl, aminocarbonylalkyl, $-\text{SR}_{46}$, and $-\text{CH}_2\text{R}_{47}$,

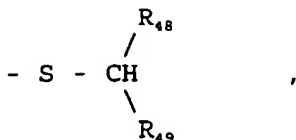
30

wherein R_{46} is selected from the group consisting of aryl (preferably substituted aryl) and heteroaryl (preferably substituted pyridyl), and

R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, tetrahydronaphthyl and benzodioxanyl; and

35

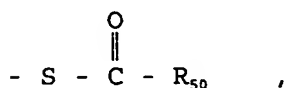
127



5

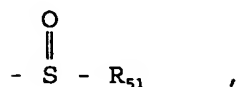
wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

10 R_{49} is selected from the group consisting of alkoxy and haloalkyl;



15

wherein R_{50} is selected from the group consisting of alkyl, alkoxy, and heteroaryl (preferably substituted heteroaryl);



20

wherein R_{51} is haloalkyl; and

25

R_6 is fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof.

30

In yet another embodiment, the novel compounds comprise a compound of Formula IIA wherein:

R_2 is fluorinated alkyl;

35

R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

40 R_4 is hydroxy, alkoxy, $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, or $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_8 is aryl and R_{10} is alkyl;

R_5 is selected from the group consisting of hydrogen, alkoxy and aryloxy; and

R_6 is selected from the group consisting of hydrogen
5 and fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof;

10 provided that when R_2 is trifluoromethyl, R_3 is selected from the group consisting of $-\text{CO}_2\text{CH}_3$ and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is hydrogen, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is selected from the group consisting of alkoxy,
15 $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, or $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_8 is aryl and R_{10} is alkyl; provided further that when R_2 , R_3 and R_5 are as defined above, and R_4 is alkoxy, then R_6 is hydrogen.

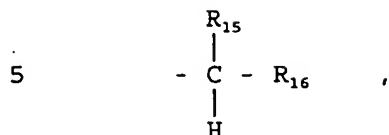
In yet another preferred embodiment, the novel
20 compounds comprise a compound of Formula IIA wherein:

R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group
25 consisting of hydrogen and alkyl;

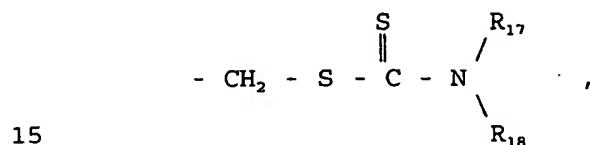
R_4 is selected from the group consisting of alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, arylthio (preferably substituted arylthio), and alkylamino; and

30 R_5 is selected from the group consisting of alkyl, arylcarbonyloxyalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl (preferably halo-substituted alkoxyalkenyl and more preferably bromo-substituted alkoxyalkenyl),
35 substituted pyrrolidinyl,

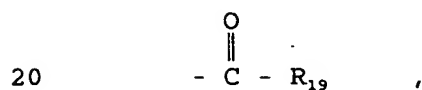


wherein R_{15} is alkoxy, and R_{16} is heteroaryl;

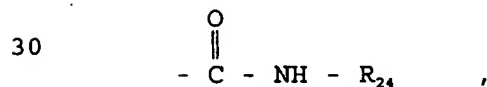
10



wherein R_{17} and R_{18} are independently alkyl;

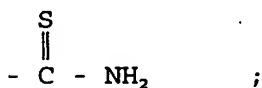


wherein R_{19} is selected from the group consisting of pyridyl, $-\text{SR}_{20}$, and $-\text{OR}_{21}$, wherein R_{20} is selected from the group consisting of aryl, heteroaryl and aminoalkyl, and R_{21} is selected from the group consisting of aryl and heteroaryl;

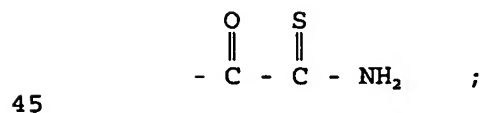


wherein R_{24} is aralkyl (preferably halo-substituted aralkyl);

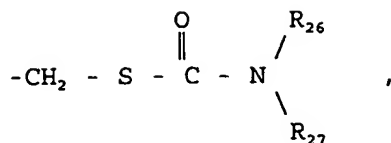
35



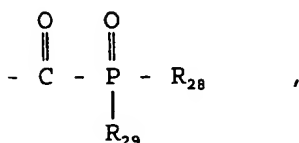
40



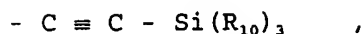
130



wherein R_{26} and R_{27} are independently alkyl;



wherein R_{28} and R_{29} are independently alkoxy; and



wherein R_{10} is alkyl; and

R_6 is selected from the group consisting of hydrogen and fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof;

provided that:

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is isopropoxy, R_5 is methyl, then R_6 is hydrogen; and

when R_5 is alkyl, then R_4 is selected from the group consisting of cycloalkyl, cycloalkylalkyl, arylthio, and alkylamino.

In yet another embodiment, the novel compounds comprise a compound of Formula IIA wherein:

131

R_2 is selected from the group consisting of fluorinated alkyl and alkoxyalkyl;

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group
5 consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of hydrogen, hydroxy, alkyl, heteroarylalkyl, thio, and trialkylsilyl;

10 R_5 is CO_2R_{14} , wherein R_{14} is alkyl; and

R_6 is selected from the group consisting of hydrogen, fluorinated alkyl, and alkoxyalkyl;

15 or a pharmaceutically acceptable salt or tautomer thereof;

provided that when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydrogen, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is selected
20 from the group consisting of hydrogen, monofluoroalkyl, and difluoroalkyl.

In yet another embodiment, the novel compounds are compounds of Formula IIA wherein:

25

R_2 is selected from the group consisting of alkyl and fluorinated alkyl;

R_3 is selected from the group consisting of $-\text{CO}_2R_7$,
30 wherein R_7 is selected from the group consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of alkyl and thio;

35

R_5 is selected from the group consisting of

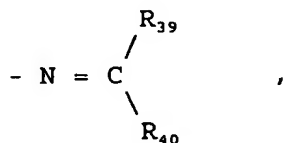
132

heterocyclyl, arylthioalkyl, heteroarylthioalkyl,

$-\text{CO}_2\text{R}_{14}$,

wherein R_{14} is alkyl;

5



10

wherein R_{39} is alkoxy, and
 R_{40} is haloalkyl;

15

$-\text{SR}_{45}$,

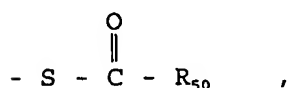
wherein R_{45} is selected from the group
 consisting of hydrogen, $-\text{SR}_{46}$, and $-\text{CH}_2\text{R}_{47}$,

20

wherein R_{46} is selected from the group
 consisting of aryl and heteroaryl, and

R_{47} is selected from the group consisting of
 methylenedioxyphenyl, pyridyl, quinolinyl, naphthyl
 and benzodioxanyl; and

25



wherein R_{50} is selected from the group
 consisting of alkyl and alkoxy; and

30

R_6 is selected from the group consisting of alkyl and
 fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer
 thereof,

35

provided that when R_2 is trifluoromethyl, R_3 is
 CO_2CH_3 , R_4 is isobutyl, and R_5 is CO_2CH_3 , then R_6 is
 selected from the group consisting of alkyl comprising at

least two carbon atoms and fluorinated alkyl.

In yet another embodiment, the novel compounds of Formula IIA are selected from the compounds listed below:

5

Methyl 5-[(4-t-Butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 180);

10

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 5);

15

Methyl 2-(Difluoromethyl)-5-(methoxycarbonylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 6);

20

Diethyl 2,6-Bis(trifluoromethyl)-4-(trimethylsilyl)-3,5-pyridinedicarboxylate (Compound 31);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(methylthiomethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 33);

25

Methyl 5-(1-Bromo-2-methoxyethenyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 35);

30

Methyl 5-(Chloroethylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 44);

35

Methyl 4-(i-Propoxy)-5-{[3-(methoxycarbonyl)-4-(i-propoxy)-6-(trifluoromethyl)-5-pyridyl]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 54);

134

Methyl 2-(Difluoromethyl)-4-cyclobutyl-5-(1-pyrrolyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 70);

5 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(aminothionocarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 77);

10 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(dimethylamino)carbonyl]thiomethyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 79);

15 Methyl 2-(Difluoromethyl)-5-[(diethylphosphono)carbonyl]-4-(i-propylamino)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 85);

Dimethyl 2,6-Bis(methoxymethyl)-4-propyl-3,5-pyridinecarboxylate (Compound 92);

20 Methyl 5-[(Aminocarbonyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 145);

25 Methyl 2-(Difluoromethyl)-5-(1-ethoxyethylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 146);

30 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(1-methoxyethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 147);

Methyl 2-(Difluoromethyl)-5-(2-fluoroethylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 148);

35

Methyl 5-(Acetylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 149);

- 5 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(2-tetrahydrofurylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 150);

- 10 Methyl 2-(Difluoromethyl)-5-{[(3,5-di-t-butylphenyl)thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 151);

- 15 Methyl 2-(Difluoromethyl)-5-{[(2,4-dimethylphenyl)thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 152);

- 20 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(2-methoxyphenyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 153);

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(3-methoxyphenyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 154);

- 25 Methyl 2-(Difluoromethyl)-5-{[(2,4-di-t-butylphenyl)thio]carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 155);

- 30 Methyl 5-{[(4-t-Butylphenyl)thio]carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 156);

- 35 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(2-isopropylphenyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 157);

136

Methyl 2-(Difluoromethyl)-5-{{(3,5-dimethylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 158);

5 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(4-methylthiophenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 159);

10 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-(4-fluorobenzyl)-4-isopropylphenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 160);

15 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-(4-fluorobenzyl)-4-fluorophenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 161);

20 Methyl 5-{{(4-chlorophenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 162);

Methyl 5-{{(2,5-Dichlorophenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 163);

25 Methyl 5-{{(2,6-Dichlorophenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 164);

30 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-naphthyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 178);

35 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(1-naphthyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 179);

137

3-Methyl 5-(3-Methoxyphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 165);

5 3-Methyl 5-(2-Nitrophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 166);

10 3-Methyl 5-(3,5-Di-t-butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 167);

15 3-Methyl 5-(2,4-Di-t-butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 168);

20 3-Methyl 5-(4-t-Butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 169);

25 3-Methyl 5-[2-(4-Fluorobenzyl)-4-isopropylphenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 170);

30 3-Methyl 5-[2-(4-Fluorobenzyl)-3,4,5-(trimethoxy)phenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 171);

35 3-Methyl 5-(2-Methoxyphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 172);

35 3-Methyl 5-(4-Chlorophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridicarboxylate (Compound 173);

3-Methyl 5-(3,5-Dimethylphenyl) 2-(Difluoromethyl)-
4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate (Compound 174);

5 3-Methyl 5-(2-Isopropylphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate (Compound 175);

10 3-Methyl 5-(2,6-Dimethyl-4-nitrophenyl) 2-
(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3,5-pyridicarboxylate (Compound 176);

15 3-Methyl 5-(2,4-Dimethylphenyl) 2-(Difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-
pyridicarboxylate (Compound 177);

20 Methyl 5-(4-t-Butylphenyldithio)-2-(difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 180);

20 Dimethyl 5,5'-Dithiobis[2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-
carboxylate] (Compound 181);

25 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)
-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]
methylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-
(trifluoromethyl)-3-pyridinecarboxylate (Compound 182);

30 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-
3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]
carbonylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-
(trifluoromethyl)-3-pyridinecarboxylate (Compound 183);

35

Methyl 5-[(3-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 184);

5 Methyl 5-[(4-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 185);

10 Methyl 5-[(2,3,5,6-Tetrafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 186);

15 Methyl 5-[(3,5-Di-*t*-butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 187);

20 Methyl 5-[(1-Methylimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 188);

Methyl 5-[(1-Methyltetrazol-5-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 189);

25 Methyl 5-[(5-Nitrobenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 190);

30 Methyl 5-[(4-(Trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 191);

35 Methyl 5-[(Quinolin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 192);

Methyl 5-[(4-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 193);

5 Methyl 5-[(Pentafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 194);

10 Methyl 5-[(2,5-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 195);

15 Methyl 5-[(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 196);

20 Methyl 5-[(4-Methylpyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 197);

Methyl 5-[(4-Nitrophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 198);

25 Methyl 5-[(4-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 199);

30 Methyl 5-[(2-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 200);

35 Methyl 5-[(2,6-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 201);

141

Methyl 5-[(Quinolin-8-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 202);

5 Methyl 5-[(Pyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 203);

10 Methyl 5-[(4-(Acetylamino)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 204);

15 Methyl 5-[(Benzoxazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 205);

20 Methyl 5-[(4-Bromo-2-(trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 206);

Methyl 5-[(3-Aminophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 207);

25 Methyl 5-[(2-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 208);

30 Methyl 5-[(5-Methylbenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 209);

35 Methyl 5-[(Benzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 210);

Methyl 5-[(3-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 211);

5 Methyl 5-[(Benzothiazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 212);

10 Methyl 5-[(3-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 213);

15 Methyl 5-[(3,4-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 214);

20 Methyl 5-[(2-Naphthyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 215);

Methyl 5-[(2-Pyridyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 216);

25 Methyl 5-[(2-bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 217);

30 Bis{3-(carbomethoxy)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-5-pyridyl)methyl Sulfide (Compound 218);

35 Methyl 5-[(2-Chloro-3,4-methylenedioxyphenyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 226);

Methyl 5-[(2-pyridyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 233);

- 5 Methyl 5-[(2-quinolinyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 241);

- 10 Methyl 5-[(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 245); and

- 15 Methyl 5[(6-chloro-1,3-benzodioxan-8-yl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 246);

- 20 Diethyl 5,5'-(Carbonyldiimino)bis[6(difluoromethyl)-4-ethyl-2-(trifluoromethyl)-3-pyridinecarboxylate (Compound 48);

- 25 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[[dimethylamino]thiono]thiomethyl-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 43);

- 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

- 30 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]carbonyl}pyridine;

- 35 2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] carbonyl} pyridine;

5 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] fluoromethyl} pyridine;

10 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] fluoromethyl} pyridine;

15 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- (2-
naphthylfluoromethyl) pyridine;

20 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] mercaptomethyl} pyridine;

2- (Difluoromethyl) -5-hydroxymethyl-4-phenyl-6-
(trifluoromethyl) -3- { [4- (trifluoromethyl) phenyl]
mercaptomethyl} pyridine;

25 2- (Cyclopentyl) -5-hydroxymethyl-4- (4-fluorophenyl) -
6- (trifluoromethyl) -3- { [4- (trifluoromethyl) phenyl]
carbonyl} pyridine;

30 2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] carbonyl} pyridine;

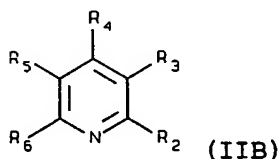
35 2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] hydroxymethyl} pyridine; and

145

2-(1-Pyrrolidinyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]fluoromethyl}pyridine.

5 In yet another embodiment, the compound of Formula IA is Dimethyl 5,5'-dithiobis[2-difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate].

10 In another embodiment, the novel compounds comprise a compound of Formula IIB:



wherein:

15 R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least
 20 one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

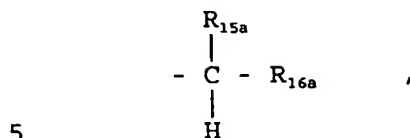
R_3 is selected from the group consisting of arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,
 25 arylalkoxyalkyl, trialkylsilyloxyalkyl,

-CHO,

-CO₂R₇,

30 wherein R_7 is selected from the group consisting of hydrogen and alkyl; and

146



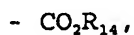
wherein R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, and

10 R_{16a} is selected from the group consisting of alkyl, haloalkyl, alkenyl, aryl and heteroaryl;

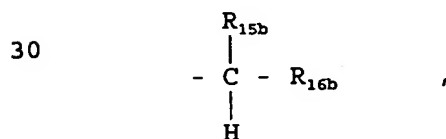
R_4 is selected from the group consisting of hydrogen, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, alkoxy, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl;

R_5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aralkyl, alkoxy, aryloxy, cycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, arylcarbonyloxyalkyl, pyrrolyl, substituted pyrrolidinyl, hydroxymethyl, arylalkoxyalkyl, and trialkylsilyloxyalkyl,

25



wherein R_{14} is alkyl;



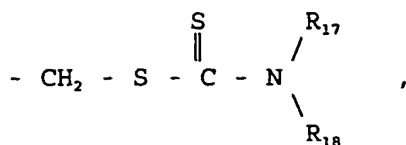
35

wherein R_{15b} is selected from the group consisting of hydroxy, halogen, alkoxy, and alkylthio, aryloxy, and alkylsulfonyloxy, and

R_{16b} is selected from the group consisting of alkyl, alkenyl, aryl, and heteroaryl;

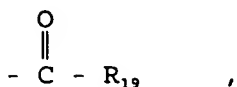
40

147



5

wherein R_{17} and R_{18} are independently alkyl;



10

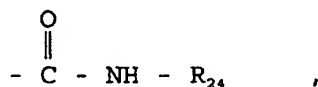
wherein R_{19} is aryl, heteroaryl, $-\text{SR}_{20}$, and $-\text{OR}_{21}$,

wherein R_{20} is selected from the group

consisting of aryl, heteroaryl and aminoalkyl, and

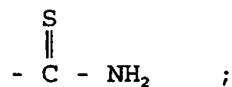
15

R_{21} is selected from the group consisting of aryl and heteroaryl;

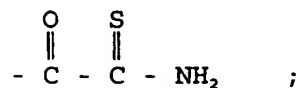


20

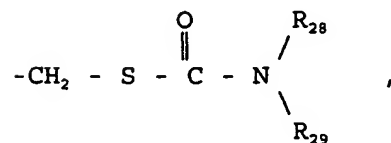
wherein R_{24} is aralkyl;



25

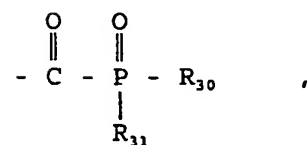


30



35

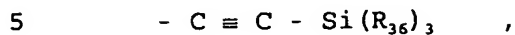
40 wherein R_{28} and R_{29} are independently alkyl;



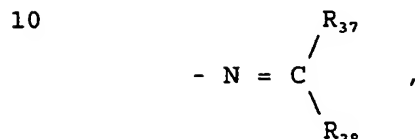
45

148

wherein R_{30} and R_{31} are independently alkoxy;

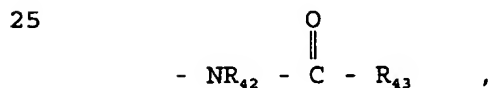


wherein R_{36} is alkyl;

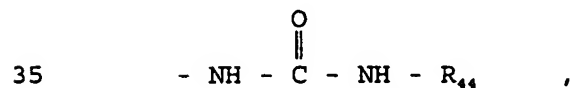


15 wherein R_{37} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

20 provided that when R_{37} is hydrogen, then R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclalkoxy;



30 wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and R_{43} is substituted heteroaryl;



wherein R_{44} is selected from the group consisting of aryl and heteroaryl;

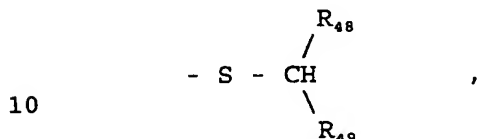


wherein R_{45} is selected from the group consisting of haloalkyl, heterocyclalkyl, alkylthioalkyl, aminocarbonylalkyl, $-SR_{46}$, and $-CH_2R_{47}$,

wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and

R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, tetrahydronaphthyl and benzodioxanyl;

5



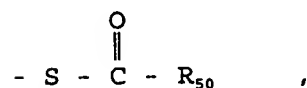
10

wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

15

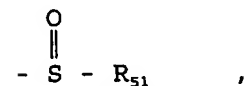
R_{49} is selected from the group consisting of alkoxy and haloalkyl;

20



wherein R_{50} is selected from the group consisting of alkyl, alkoxy, and heteroaryl; and

25



wherein R_{51} is haloalkyl;

or a pharmaceutically acceptable salt or tautomer thereof,

30

provided that:

when R_2 is selected from the group consisting of difluoromethyl and trifluoromethyl, R_3 is selected from the group consisting of $-CO_2H$, $-CO_2CH_3$, and $-CO_2C_2H_5$, R_5 is hydrogen, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is selected from the group consisting of cycloalkyl, cycloalkylalkyl,

35

heteroarylalkyl, aralkenyl, alkoxy, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl; provided further that when R_2 , R_3 and R_5 are as defined above, and R_4 is alkoxy, then R_6 is hydrogen;

5

when R_2 is selected from the group consisting of fluorinated methyl and chlorofluorinated methyl, R_3 is selected from the group consisting of hydroxymethyl and CO_2R_7 , R_5 is selected from the group consisting of hydroxymethyl and CO_2R_{14} , R_6 is selected from the group consisting of fluorinated methyl and chlorofluorinated methyl, and R_7 and R_{14} are independently alkyl, then R_4 is selected from the group consisting of thio, trialkylsilyl, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl;

15

when R_2 is difluoromethyl, R_3 is $-CO_2C_2H_5$, R_4 is hydrogen, R_5 is $-CO_2C_2H_5$, then R_6 is selected from the group consisting of hydrogen, monofluoroalkyl, difluoroalkyl and alkoxyalkyl;

20

when R_2 is trifluoromethyl, R_3 is $-CO_2R_7$, R_5 is methyl, R_6 is selected from the group consisting of fluorinated methyl, fluorinated ethyl and chlorofluorinated methyl, and R_7 is selected from the group consisting of hydrogen and alkyl, then R_4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl;

25

when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_3 is $-CO_2R_7$, and R_7 is alkyl, then R_5 is other than arylcarbonyl, heteroarylcarbonyl or

30

151

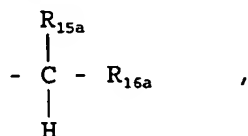


wherein R_{16b} is alkyl when R_{15b} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16b} is aryl or heteroaryl when R_{15b} is hydroxy;

10

when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_5 is $-CO_2R_{14}$, and R_{14} is alkyl, then R_3 is other than arylcarbonyl, heteroarylcarbonyl or

15



20

wherein R_{16a} is alkyl when R_{15a} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16a} is aryl or heteroaryl when R_{15a} is hydroxy; and

25

when R_2 and R_6 are independently selected from fluorinated methyl and chlorofluorinated methyl, R_3 is CO_2R_7 , R_5 is hydroxy, alkoxy or aryloxy, then R_4 is selected from the group consisting of aryl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl; and

30

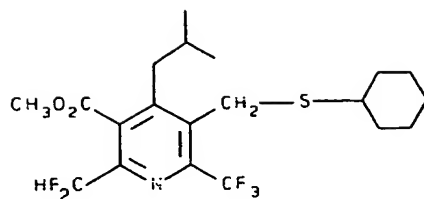
when R_4 is aryl and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.

35

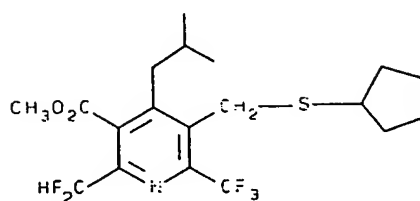
Additional Compounds

Additional novel compounds that could be used in the methods and compositions of the present invention include, but are not limited to, the compounds:

152

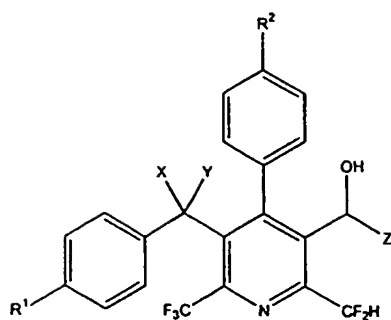


and



and those compounds listed in Tables 9, 10, 11 and 12
5 below. These compounds could be prepared by appropriate
modification of the synthetic schemes previously
referenced in this application.

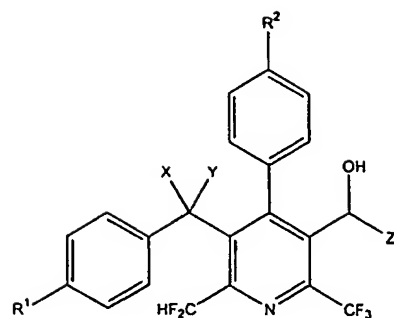
Table 9



<u>R¹</u>	<u>R²</u>	<u>X</u>	<u>Y</u>	<u>Z</u>
Cl	H	H	OH	H
<i>i</i> Pr	H	H	OH	H
F	H	H	OH	H
CF ₃	H	H	OH	H
Cl	H	O	O	H
<i>i</i> Pr	H	O	O	H
F	H	O	O	H
CF ₃	H	O	O	H
Cl	H	F	H	H
<i>i</i> Pr	H	F	H	H
F	H	F	H	H
CF ₃	H	F	H	H
Cl	H	H	OH	CH ₃
<i>i</i> Pr	H	H	OH	CH ₃
F	H	H	OH	CH ₃
CF ₃	H	H	OH	CH ₃
Cl	H	O	O	CH ₃
<i>i</i> Pr	H	O	O	CH ₃
F	H	O	O	CH ₃
CF ₃	H	O	O	CH ₃
Cl	H	F	H	CH ₃
<i>i</i> Pr	H	F	H	CH ₃
F	H	F	H	CH ₃
CF ₃	H	F	H	CH ₃
Cl	H	H	OH	C ₂ H ₅
<i>i</i> Pr	H	H	OH	C ₂ H ₅
F	H	H	OH	C ₂ H ₅
CF ₃	H	H	OH	C ₂ H ₅

Cl	H	O	O	C ₂ H ₅
<i>i</i> Pr	H	O	O	C ₂ H ₅
F	H	O	O	C ₂ H ₅
CF ₃	H	O	O	C ₂ H ₅
Cl	H	F	H	C ₂ H ₅
<i>i</i> Pr	H	F	H	C ₂ H ₅
F	H	F	H	C ₂ H ₅
CF ₃	H	F	H	C ₂ H ₅
Cl	H	H	OH	<i>i</i> Bu
<i>i</i> Pr	H	H	OH	<i>i</i> Bu
F	H	H	OH	<i>i</i> Bu
CF ₃	H	H	OH	<i>i</i> Bu
Cl	H	O	O	<i>i</i> Bu
<i>i</i> Pr	H	O	O	<i>i</i> Bu
F	H	O	O	<i>i</i> Bu
CF ₃	H	O	O	<i>i</i> Bu
Cl	H	F	H	<i>i</i> Bu
<i>i</i> Pr	H	F	H	<i>i</i> Bu
F	H	F	H	<i>i</i> Bu
CF ₃	H	F	H	<i>i</i> Bu
Cl	H	H	OH	CF ₃
<i>i</i> Pr	H	H	OH	CF ₃
F	H	H	OH	CF ₃
CF ₃	H	H	OH	CF ₃
Cl	H	O	O	CF ₃
<i>i</i> Pr	H	O	O	CF ₃
F	H	O	O	CF ₃
CF ₃	H	O	O	CF ₃
Cl	H	F	H	CF ₃
<i>i</i> Pr	H	F	H	CF ₃
F	H	F	H	CF ₃
CF ₃	H	F	H	CF ₃

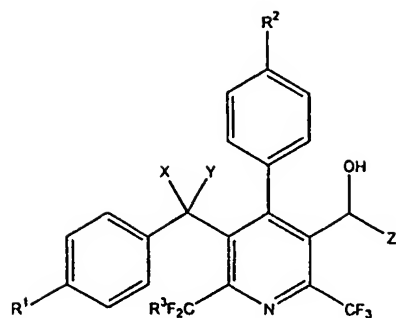
Table 10



<u>R¹</u>	<u>R²</u>	<u>X</u>	<u>Y</u>	<u>Z</u>
Cl	H	H	OH	H
iPr	H	H	OH	H
F	H	H	OH	H
CF ₃	H	H	OH	H
Cl	H	O	O	H
iPr	H	O	O	H
F	H	O	O	H
CF ₃	H	O	O	H
Cl	H	F	H	H
iPr	H	F	H	H
F	H	F	H	H
CF ₃	H	F	H	H
Cl	H	H	OH	CH ₃
iPr	H	H	OH	CH ₃
F	H	H	OH	CH ₃
CF ₃	H	H	OH	CH ₃
Cl	H	O	O	CH ₃
iPr	H	O	O	CH ₃
F	H	O	O	CH ₃
CF ₃	H	O	O	CH ₃
Cl	H	F	H	CH ₃
iPr	H	F	H	CH ₃
F	H	F	H	CH ₃
CF ₃	H	F	H	CH ₃
Cl	H	H	OH	C ₂ H ₅
iPr	H	H	OH	C ₂ H ₅
F	H	H	OH	C ₂ H ₅
CF ₃	H	H	OH	C ₂ H ₅

Cl	H	O	O	C ₂ H ₅
<i>i</i> Pr	H	O	O	C ₂ H ₅
F	H	O	O	C ₂ H ₅
CF ₃	H	O	O	C ₂ H ₅
Cl	H	F	H	C ₂ H ₅
<i>i</i> Pr	H	F	H	C ₂ H ₅
F	H	F	H	C ₂ H ₅
CF ₃	H	F	H	C ₂ H ₅
Cl	H	H	OH	<i>i</i> Bu
<i>i</i> Pr	H	H	OH	<i>i</i> Bu
F	H	H	OH	<i>i</i> Bu
CF ₃	H	H	OH	<i>i</i> Bu
Cl	H	O	O	<i>i</i> Bu
<i>i</i> Pr	H	O	O	<i>i</i> Bu
F	H	O	O	<i>i</i> Bu
CF ₃	H	O	O	<i>i</i> Bu
Cl	H	F	H	<i>i</i> Bu
<i>i</i> Pr	H	F	H	<i>i</i> Bu
F	H	F	H	<i>i</i> Bu
CF ₃	H	F	H	<i>i</i> Bu
Cl	H	H	OH	CF ₃
<i>i</i> Pr	H	H	OH	CF ₃
F	H	H	OH	CF ₃
CF ₃	H	H	OH	CF ₃
Cl	H	O	O	CF ₃
<i>i</i> Pr	H	O	O	CF ₃
F	H	O	O	CF ₃
CF ₃	H	O	O	CF ₃
Cl	H	F	H	CF ₃
<i>i</i> Pr	H	F	H	CF ₃
F	H	F	H	CF ₃
CF ₃	H	F	H	CF ₃

Table 11

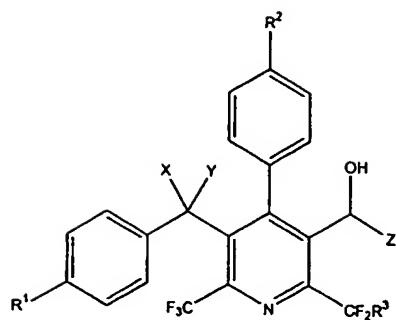


<u>R¹</u>	<u>R²</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R³</u>
Cl	H	H	OH	H	CH₃
iPr	H	H	OH	H	CH₃
F	H	H	OH	H	CH₃
CF₃	H	H	OH	H	CH₃
Cl	H	O	O	H	CH₃
iPr	H	O	O	H	CH₃
F	H	O	O	H	CH₃
CF₃	H	O	O	H	CH₃
Cl	H	F	H	H	CH₃
iPr	H	F	H	H	CH₃
F	H	F	H	H	CH₃
CF₃	H	F	H	H	CH₃
Cl	H	H	OH	CH₃	CH₃
iPr	H	H	OH	CH₃	CH₃
F	H	H	OH	CH₃	CH₃
CF₃	H	H	OH	CH₃	CH₃
Cl	H	O	O	CH₃	CH₃
iPr	H	O	O	CH₃	CH₃
F	H	O	O	CH₃	CH₃
CF₃	H	O	O	CH₃	CH₃
Cl	H	F	H	CH₃	CH₃
iPr	H	F	H	CH₃	CH₃
F	H	F	H	CH₃	CH₃
CF₃	H	F	H	CH₃	CH₃
Cl	H	H	OH	C₂H₅	CH₃
iPr	H	H	OH	C₂H₅	CH₃
F	H	H	OH	C₂H₅	CH₃
CF₃	H	H	OH	C₂H₅	CH₃

Cl	H	O	O	C ₂ H ₅	CH ₃
iPr	H	O	O	C ₂ H ₅	CH ₃
F	H	O	O	C ₂ H ₅	CH ₃
CF ₃	H	O	O	C ₂ H ₅	CH ₃
Cl	H	F	H	C ₂ H ₅	CH ₃
iPr	H	F	H	C ₂ H ₅	CH ₃
F	H	F	H	C ₂ H ₅	CH ₃
CF ₃	H	F	H	C ₂ H ₅	CH ₃
iPr	H	H	OH	C ₂ H ₅	CH ₃
F	H	H	OH	iBu	CH ₃
CF ₃	H	H	OH	iBu	CH ₃
Cl	H	O	O	iBu	CH ₃
iPr	H	O	O	iBu	CH ₃
F	H	O	O	iBu	CH ₃
CF ₃	H	O	O	iBu	CH ₃
Cl	H	F	H	iBu	CH ₃
iPr	H	F	H	iBu	CH ₃
F	H	F	H	iBu	CH ₃
CF ₃	H	F	H	iBu	CH ₃
Cl	H	H	OH	iBu	CH ₃
iPr	H	H	OH	CF ₃	CH ₃
F	H	H	OH	CF ₃	CH ₃
CF ₃	H	H	OH	CF ₃	CH ₃
Cl	H	O	O	CF ₃	CH ₃
iPr	H	O	O	CF ₃	CH ₃
F	H	O	O	CF ₃	CH ₃
CF ₃	H	O	O	CF ₃	CH ₃
Cl	H	F	H	CF ₃	CH ₃
iPr	H	F	H	CF ₃	CH ₃
F	H	F	H	CF ₃	CH ₃
CF ₃	H	F	H	CF ₃	CH ₃
Cl	H	H	OH	CF ₃	CH ₃
iPr	H	H	OH	H	Ph
F	H	H	OH	H	Ph
CF ₃	H	H	OH	H	Ph
Cl	H	H	OH	H	Ph
iPr	H	O	O	H	Ph
F	H	O	O	H	Ph
CF ₃	H	O	O	H	Ph
Cl	H	F	H	H	Ph
iPr	H	F	H	H	Ph
F	H	F	H	H	Ph
CF ₃	H	F	H	H	Ph
Cl	H	H	OH	H	Ph
iPr	H	H	OH	CH ₃	Ph
F	H	H	OH	CH ₃	Ph
				CH ₃	Ph

CF ₃	H	H	OH	CH ₃	Ph
Cl	H	O	O	CH ₃	Ph
iPr	H	O	O	CH ₃	Ph
F	H	O	O	CH ₃	Ph
CF ₃	H	O	O	CH ₃	Ph
Cl	H	F	H	CH ₃	Ph
iPr	H	F	H	CH ₃	Ph
F	H	F	H	CH ₃	Ph
CF ₃	H	F	H	CH ₃	Ph
Cl	H	H	OH	CH ₃	Ph
iPr	H	H	OH	C ₂ H ₅	Ph
F	H	H	OH	C ₂ H ₅	Ph
CF ₃	H	H	OH	C ₂ H ₅	Ph
Cl	H	O	O	C ₂ H ₅	Ph
iPr	H	O	O	C ₂ H ₅	Ph
F	H	O	O	C ₂ H ₅	Ph
CF ₃	H	O	O	C ₂ H ₅	Ph
Cl	H	F	H	C ₂ H ₅	Ph
iPr	H	F	H	C ₂ H ₅	Ph
F	H	F	H	C ₂ H ₅	Ph
CF ₃	H	F	H	C ₂ H ₅	Ph
iPr	H	H	OH	C ₂ H ₅	Ph
F	H	H	OH	iBu	Ph
CF ₃	H	H	OH	iBu	Ph
Cl	H	O	O	iBu	Ph
iPr	H	O	O	iBu	Ph
F	H	O	O	iBu	Ph
CF ₃	H	O	O	iBu	Ph
Cl	H	F	H	iBu	Ph
iPr	H	F	H	iBu	Ph
F	H	F	H	iBu	Ph
CF ₃	H	F	H	iBu	Ph
Cl	H	H	OH	H	CF ₃
iPr	H	H	OH	H	CF ₃
F	H	H	OH	H	CF ₃
CF ₃	H	H	OH	H	CF ₃
Cl	H	O	O	H	CF ₃
iPr	H	O	O	H	CF ₃
F	H	O	O	H	CF ₃
CF ₃	H	O	O	H	CF ₃
Cl	H	F	H	H	CF ₃
iPr	H	F	H	H	CF ₃
F	H	F	H	H	CF ₃
CF ₃	H	F	H	H	CF ₃

Table 12



<u>R¹</u>	<u>R²</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R³</u>
Cl	H	H	OH	H	CH ₃
<i>i</i> Pr	H	H	OH	H	CH ₃
F	H	H	OH	H	CH ₃
CF ₃	H	H	OH	H	CH ₃
Cl	H	O	O	H	CH ₃
<i>i</i> Pr	H	O	O	H	CH ₃
F	H	O	O	H	CH ₃
CF ₃	H	O	O	H	CH ₃
Cl	H	F	H	H	CH ₃
<i>i</i> Pr	H	F	H	H	CH ₃
F	H	F	H	H	CH ₃
CF ₃	H	F	H	H	CH ₃
Cl	H	H	OH	CH ₃	CH ₃
<i>i</i> Pr	H	H	OH	CH ₃	CH ₃
F	H	H	OH	CH ₃	CH ₃
CF ₃	H	H	OH	CH ₃	CH ₃
Cl	H	O	O	CH ₃	CH ₃
<i>i</i> Pr	H	O	O	CH ₃	CH ₃
F	H	O	O	CH ₃	CH ₃
CF ₃	H	O	O	CH ₃	CH ₃
Cl	H	F	H	CH ₃	CH ₃
<i>i</i> Pr	H	F	H	CH ₃	CH ₃
F	H	F	H	CH ₃	CH ₃
CF ₃	H	F	H	CH ₃	CH ₃
Cl	H	H	OH	CH ₃	CH ₃
<i>i</i> Pr	H	H	OH	C ₂ H ₅	CH ₃
F	H	H	OH	C ₂ H ₅	CH ₃
CF ₃	H	H	OH	C ₂ H ₅	CH ₃

Cl	H	O	O	C ₂ H ₅	CH ₃
<i>i</i> Pr	H	O	O	C ₂ H ₅	CH ₃
F	H	O	O	C ₂ H ₅	CH ₃
CF ₃	H	O	O	C ₂ H ₅	CH ₃
Cl	H	F	H	C ₂ H ₅	CH ₃
<i>i</i> Pr	H	F	H	C ₂ H ₅	CH ₃
F	H	F	H	C ₂ H ₅	CH ₃
CF ₃	H	F	H	C ₂ H ₅	CH ₃
<i>i</i> Pr	H	H	OH	C ₂ H ₅	CH ₃
F	H	H	OH	<i>i</i> Bu	CH ₃
CF ₃	H	H	OH	<i>i</i> Bu	CH ₃
Cl	H	O	O	<i>i</i> Bu	CH ₃
<i>i</i> Pr	H	O	O	<i>i</i> Bu	CH ₃
F	H	O	O	<i>i</i> Bu	CH ₃
CF ₃	H	O	O	<i>i</i> Bu	CH ₃
Cl	H	F	H	<i>i</i> Bu	CH ₃
<i>i</i> Pr	H	F	H	<i>i</i> Bu	CH ₃
F	H	F	H	<i>i</i> Bu	CH ₃
CF ₃	H	F	H	<i>i</i> Bu	CH ₃
Cl	H	H	OH	<i>i</i> Bu	CH ₃
<i>i</i> Pr	H	H	OH	CF ₃	CH ₃
F	H	H	OH	CF ₃	CH ₃
CF ₃	H	H	OH	CF ₃	CH ₃
Cl	H	O	O	CF ₃	CH ₃
<i>i</i> Pr	H	O	O	CF ₃	CH ₃
F	H	O	O	CF ₃	CH ₃
CF ₃	H	O	O	CF ₃	CH ₃
Cl	H	F	H	CF ₃	CH ₃
<i>i</i> Pr	H	F	H	CF ₃	CH ₃
F	H	F	H	CF ₃	CH ₃
CF ₃	H	F	H	CF ₃	CH ₃
Cl	H	H	OH	CF ₃	CH ₃
<i>i</i> Pr	H	H	OH	H	Ph
F	H	H	OH	H	Ph
CF ₃	H	H	OH	H	Ph
Cl	H	H	OH	H	Ph
<i>i</i> Pr	H	O	O	H	Ph
F	H	O	O	H	Ph
CF ₃	H	O	O	H	Ph
Cl	H	O	O	H	Ph
<i>i</i> Pr	H	F	H	H	Ph
F	H	F	H	H	Ph
CF ₃	H	F	H	H	Ph
Cl	H	F	H	H	Ph
<i>i</i> Pr	H	H	OH	H	Ph
F	H	H	OH	CH ₃	Ph
			OH	CH ₃	Ph
			OH	CH ₃	Ph

CF ₃	H	H	OH	CH ₃	Ph
Cl	H	O	O	CH ₃	Ph
iPr	H	O	O	CH ₃	Ph
F	H	O	O	CH ₃	Ph
CF ₃	H	O	O	CH ₃	Ph
Cl	H	F	H	CH ₃	Ph
iPr	H	F	H	CH ₃	Ph
F	H	F	H	CH ₃	Ph
CF ₃	H	F	H	CH ₃	Ph
Cl	H	H	OH	C ₂ H ₅	Ph
iPr	H	H	OH	C ₂ H ₅	Ph
F	H	H	OH	C ₂ H ₅	Ph
CF ₃	H	H	OH	C ₂ H ₅	Ph
Cl	H	O	O	C ₂ H ₅	Ph
iPr	H	O	O	C ₂ H ₅	Ph
F	H	O	O	C ₂ H ₅	Ph
CF ₃	H	O	O	C ₂ H ₅	Ph
Cl	H	F	H	C ₂ H ₅	Ph
iPr	H	F	H	C ₂ H ₅	Ph
F	H	F	H	C ₂ H ₅	Ph
CF ₃	H	F	H	C ₂ H ₅	Ph
iPr	H	H	OH	iBu	Ph
F	H	H	OH	iBu	Ph
CF ₃	H	H	OH	iBu	Ph
Cl	H	O	O	iBu	Ph
iPr	H	O	O	iBu	Ph
F	H	O	O	iBu	Ph
CF ₃	H	O	O	iBu	Ph
Cl	H	F	H	iBu	Ph
iPr	H	F	H	iBu	Ph
F	H	F	H	iBu	Ph
CF ₃	H	F	H	iBu	Ph
Cl	H	H	OH	H	CF ₃
iPr	H	H	OH	H	CF ₃
F	H	H	OH	H	CF ₃
CF ₃	H	H	OH	H	CF ₃
Cl	H	O	O	H	CF ₃
iPr	H	O	O	H	CF ₃
F	H	O	O	H	CF ₃
CF ₃	H	O	O	H	CF ₃
Cl	H	F	H	H	CF ₃
iPr	H	F	H	H	CF ₃
F	H	F	H	H	CF ₃
CF ₃	H	F	H	H	CF ₃

Pharmaceutical Compositions

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of Formulae I, IA, IB and/or Formulae IIA or IIB in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

The phrase "co-therapy" (or combination-therapy), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent. The compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in co-therapy with one or more cardiovascular agents, such as compounds that lower serum cholesterol concentrations including inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors such as the statins (atorvastatin, cerivastatin, pravastatin, simvastatin, fluvastatin and lovastatin), inhibitors of squalene synthase, oxido squalene cyclase or inhibitors of other enzymes involved with cholesterol biosynthesis; inhibitors of the ileal

bile acid transport protein (IBAT), cholesterol absorption antagonists, ACAT inhibitors, bile acid sequestrants such as Cholestyramine and Cholestagel, fibrates such as Gemfibrozil, niacins such as Niaspan, and omega-3 fatty acids such as Omacor. Compounds of the present invention can also be used in co-therapy with cardiovascular drugs that reduce hypertension such as Enalapril and Captopril, or with anti-diabetes drugs such as troglitazone, or with antithrombotic agents such as aspirin, warfarin, and glycoprotein IIb/IIIa antagonists such as Reopro, Xemilofiban and Orbofiban. The compounds of this invention can also be used in co-therapy with agents which lower serum triglyceride concentrations, including inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors such as the statins (atorvastatin), fibrates such as Gemfibrozil, niacins such as Niaspan, and omega-3 fatty acids such as Omacor.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent which will achieve the goal of improvement in disease severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions

of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. Patients undergoing treatment with the compounds and/or compositions disclosed herein can be routinely monitored by conventional methods to determine the effectiveness of therapy. Continuous analysis of the data obtained permits modification of the treatment regimen during treatment so that optimal amounts of the compounds and/or compositions of this invention are administered, and so that the duration of treatment can be determined as well. Thus, the treatment regimen/dosing schedule can be rationally modified over the course of treatment so as to achieve the lowest doses of each of the compounds and/or compositions of this invention which together result in satisfactory anti-lipidemic effectiveness, and so that administration of these compounds is continued only so long as is necessary to successfully treat the patient.

The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase

of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the

formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the
5 formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable
10 product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl
15 palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other
20 mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active
25 ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

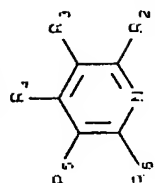
For therapeutic purposes, the active compounds of
30 this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose
35 alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric

and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

20 Additional Substituted Pyridines

The present invention further includes a group of substituted pyridines which exhibit percentage transfers in excess of 100% and are useful (i) in examining the structural requirements of the active site of the CTEP molecule, (ii) as control pyridines in the study of the mechanism for inhibiting the activity of CETP, and (ii) in the design of substituted pyridines which are effective CETP inhibitors. Accordingly, they are useful in studying the prevention and treatment of dyslipidemia (hypoalphalipoproteinaemia), hyperlipoproteinaemia (chylomicronemia and hyperapobetalipoproteinaemia), peripheral vascular disease, hypercholesterolemia, atherosclerosis, coronary artery disease and other CETP-mediated disorders. These substituted pyridines include those compounds listed in Table 13 below:

TABLE 13



CP	R_2	R_1	R_4	R_5	R_6
300	OCH_3	H	H	CO_2H	H
301	CF_3H	CO_2CH_3	i-Bu	$NHC(O)CH_2Br$	CF_3
302	CF_3	H	CF_3	$CO_2C_2H_5$	$CH_2CO_2C_2H_5$
303	CF_3H	CO_2CH_3	i-Pr	$C(O)N(CH_3)OCH_3$	CF_3
304	NH_2	CO_2H	H	H	H
305	CH_3	$CO_2C_2H_5$	H	$CO_2C_2H_5$	CH_3
306	CF_3	$CO_2C_2H_5$	Et	CN	CF_2H
307	CF_3	CO_2CH_3	O-i-Pr	$S(O)Ph$	CF_3
308	$CH_2CO_2C_2H_5$	$CO_2C_2H_5$	H	H	H
309	CF_3	CO_2CH_3	OH	SPh	CF_3
310	CF_2Cl	CO_2CH_3	1-azyridinyl	$CO_2C_2H_5$	CF_3
311	CF_3	CO_2CH_3	$OC(O)-(4-CF_3-Ph)$	H	CF_3
312	CO_2H	H	H	H	CO_2H
313	CF_3	CO_2CH_3	i-Bu	CO_2CH_3	CH_3
314	CF_2H	$CO_2C_2H_5$	H	$CO_2C_2H_5$	CF_3
315	CF_3	$CO_2C_2H_5$	$OCH_2CH=CH_2$	H	CF_3
316	CF_2H	$CON(CH_3)_2$	i-Bu	CO_2CH_3	CF_3
317	CF_2H	CO_2H	$CH=C(CH_3)_2$	CN	CF_3
318	CF_3	CO_2CH_3	$OC(O)-Pr$	H	CF_3
319	CF_3	CO_2CH_3	O-(4-Cl-Ph)	H	CF_3
320	CF_2H	CO_2CH_3	NH-i-Pr	$C(O)-1-pyrazolyl$	CF_3
321	CF_3	$CO_2C_2H_5$	OH	CH_3	H
322	CH_3	$CO_2C_2H_5$	H	$C(O)NHCH_2-(4-Cl-Ph)$	CH_3

CP	R ₂	R ₁	R ₄	R ₃	R ₆
323	CF ₃ H	CO ₂ CH ₃	Pr	C(O)NH(CH ₂) ₂ Cl	CF ₃
324	CF ₃	CO ₂ CH ₃	OC(O)-t-Bu	H	CF ₃
325	CF ₃ H	CO ₂ H	CH=C(CH ₃) ₂	CO ₂ CH ₃	CF ₃
326	CF ₃ H	CO ₂ CH ₃	N=S(CH ₃) ₂	CO ₂ C ₂ H ₅	CF ₃
327	OH	CO ₂ H	H	H	CH ₃
328	CF ₃ H	CO ₂ CH ₃	Pr	C(O)N(CH ₃)OCH ₃	CF ₃
329	CF ₃	CO ₂ C ₂ H ₅	OH	H	H
330	CF ₃ H	CO ₂ CH ₃	i-Bu	NHC(O)CH ₃	CF ₃
331	H	CO ₂ CH ₃	H	H	OCH ₃
332	CF ₃	CO ₂ H	OH	CH ₃	CF ₃
333	CF ₃ H	CO ₂ CH ₃	i-Bu	C(O)NH(CH ₂) ₂ OH	CF ₃
334	CH ₃	CO ₂ CH ₃	CF ₃	H	CH ₃
335	CF ₃	CO ₂ CH ₃	CH ₃ -c-Pr	NHCO ₂ CH ₃	CF ₃
336	CF ₃ H	CO ₂ CH ₃	O(CO)-	2-oxazoliny	CF ₃
337	CF ₃	CO ₂ CH ₃	(pentafluorophenyl)	H	CF ₃
338	CF ₃ H	CO ₂ CH ₃	i-Bu	C(SCH ₃)=NCH ₂ Ph	CF ₃
339	CH ₃	CO ₂ C ₂ H ₅	O-i-Pr	CO ₂ C ₂ H ₅	CH ₃
340	CF ₃ H	CO ₂ H	CH ₂ SCH ₃	CO ₂ C ₂ H ₅	CF ₃
341	CF ₃	CO ₂ CH ₃	i-Bu	CO ₂ CH ₃	CH(1-morpholinyl) ₂
342	CF ₃ H	CO ₂ CH ₃	i-Pr	C(O)NH(CH ₂) ₂ OH	CF ₃
343	CF ₃ H	CONHCH ₃	i-Pr	CO ₂ C ₂ H ₅	CF ₃
344	CF ₃ H	CO ₂ CH ₃	CH ₂ S ⁺ (CH ₃) ₂	CO ₂ C ₂ H ₅	CF ₃
345	CF ₃	Si(CH ₃) ₃	BF ₄ ⁻	CO ₂ CH ₃	CF ₃
346	CF ₃ H	CO ₂ CH ₃	OCH ₃	C(O)N(CH ₃) ₂	CF ₃
347	CH ₃	CO ₂ CH ₃	i-Pr	CO ₂ CH ₃	CH ₂ Cl
348	CH ₃	CO ₂ C ₂ H ₅	i-Bu	OS(O) ₂ -(4-	CH ₃
349	CF ₃	CO ₂ H	CO ₂ C ₂ H ₅	CH ₃ Ph)	CF ₃
350	CF ₃ H	CO ₂ CH ₃	H	H	CF ₃
			i-Bu		CF ₃

Definitions and Abbreviations

The use of generic terms and abbreviations in the description of the compounds are herein defined for clarity.

- 5 The term "alkyl", either alone or within other terms such as "haloalkyl", "cyanoalkyl" and "alkylthio", embraces substituted or unsubstituted linear or branched radicals having one to about 10 carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals
10 having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and the like. The term "higher alkyl" denotes linear or branched radicals having eleven to about twenty carbon atoms.
15 Examples of such radicals include undecyl, dodecyl, tridecyl, tetradecyl, and pentadecyl.

- The term "alkenyl", either alone or within other terms such as "haloalkenyl" and "alkenylthio", embraces substituted or unsubstituted linear or branched radicals
20 having one to about 10 carbon atoms and having one or more double bonds. More preferred alkenyl radicals are "lower alkenyl" radicals having one to about six carbon atoms. Examples of such radicals include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and
25 the like. The term "higher alkenyl" denotes linear or branched radicals having from 11 to about 20 carbon atoms and having one or more double bonds. Examples of such radicals include undecenyl, dodecenyl, tridecenyl, tetradecenyl, and pentadecenyl. Preferably, the
30 unsaturation is remote from the moiety attaching the alkenyl group to the pyridine ring.

- The term "alkynyl", either alone or within other terms such as "haloalkynyl" and "alkynylthio", embraces substituted or unsubstituted linear or branched radicals
35 having one to about 10 carbon atoms and having one or more triple bonds. More preferred alkynyl radicals are

"lower alkynyl" radicals having one to about six carbon atoms. Examples of such radicals include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like. The term "higher alkynyl" denotes linear or branched radicals having from 11 to about 20 carbon atoms having one or more triple bonds. Examples of such radicals include undecynyl, dodecynyl, tridecynyl, tetradecynyl, and pentadecynyl. Preferably, the unsaturation is remote from the moiety attaching the alkynyl group to the pyridine ring.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane, anthryl and biphenyl. Said "aryl" group can be substituted or unsubstituted.

The term "heterocyclyl" embraces saturated or partially saturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Partially saturated heterocyclyl radicals have at least one double bond, but less than the maximum number of double bonds possible for the heterocyclyl ring. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. azyrindinyl, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 oxygen atoms [e.g. oxiranyl, oxolanyl, dioxolanyl, dioxanyl, etc.]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 sulfur atoms [e.g. thiolanyl, dithiolanyl, dithianyl, etc.]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. oxazolidinyl, morpholinyl, etc.]; saturated 3 to 6-membered

heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]; and saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 oxygen atoms [e.g., oxathiolanyl, etc.]. Examples of partially saturated heterocyclyl radicals include imidazoliny, oxazoliny, isoxazoliny, thiazoliny, isothiazoliny, dihydrothiophene, dihydropyran and dihydrofuran. Heterocyclic radicals also encompass unsaturated or partially saturated condensed heterocyclic radicals such as benzodioxanyl. Heterocyclyl radicals further can be unsubstituted or substituted with one or more groups including, for example, alkyl, halo, alkoxy, nitro, trifluoromethoxy, cycloalkyl, haloalkyl, alkylthio, alkylidene, acylamino, aryloxy, arylalkoxy, and oxo.

The term "heteroaryl" embraces unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Heteroaryl radicals have the maximum number of double bonds possible for the heterocyclyl ring. Examples of heteroaryl radicals include unsaturated 5 to 6 membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, triazolyl, tetrazolyl, etc.; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl and benzotriazolyl, etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl and isoxazolyl, etc.; unsaturated condensed

heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, isothiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents such as, for example, lower alkyl, lower alkoxy, halo, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. Heteroaryl can be unsubstituted or substituted with one or more groups selected from, for example, alkyl, halo, alkoxy, nitro, trifluoro-methoxy, cycloalkyl, haloalkyl, alkylthio, alkylidene, acylamino, aryloxy, arylalkoxy, and oxo.

The term "cycloalkyl" embraces substituted or unsubstituted radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of

such radicals include cyclopropylmethyl and cyclohexylhexyl. Also preferred cycloalkylalkyl radicals are "higher cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having seven to fifteen carbon atoms. Examples of such radicals include cyclohexyldodecyl.

The term "cycloalkenyl" embraces radicals having three to ten carbon atoms and one or more carbon-carbon double bonds. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. Said "aryl" group may have 1 to 3 substituents such as, for example, lower alkyl, alkoxy, halo, hydroxy, oxo, amino and lower alkylamino.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. Also preferred aralkyl radicals are "higher aralkyl" radicals having aryl radicals attached to alkyl radicals having seven to fifteen carbon atoms. Examples of such radicals include phenyloctyl and phenylundecyl. The aryl in said aralkyl may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are used herein interchangeably.

The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals. Preferable heteroaralkyl radicals are "lower heteroaralkyl" radicals having heteroaryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include -CH(OH)-2-furyl; -CH(OH)-2-thienyl; -CH(OCH₃)-2-thienyl; and -CH(OCH₃)-(5-isothiazolyl). Also

preferred heteroaralkyl radicals are "higher heteroaralkyl" radicals having heteroaryl radicals attached to alkyl radicals having seven to fifteen carbon atoms. The heteroaryl in said heteroaralkyl may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "heterocyclalkyl" embraces heterocycl-substituted alkyl radicals. Preferable heterocyclalkyl radicals are "lower heterocyclalkyl" radicals having heterocycl radicals attached to alkyl radicals having one to six carbon atoms. An examples of such radicals is $-\text{CH}_2-(2\text{-thiazolinyl})$. Also preferred heterocyclalkyl radicals are "higher heterocyclalkyl" radicals having heterocycl radicals attached to alkyl radicals having seven to fifteen carbon atoms. The heterocycl radical in said heterocyclalkyl may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "aralkenyl" embraces aryl-substituted alkenyl radicals. Preferable aralkenyl radicals are "lower aralkenyl" radicals having aryl radicals attached to alkenyl radicals having one to six carbon atoms. Examples of such radicals include $-\text{CH}=\text{C}(\text{CH}_3)\text{Ph}$. Also preferred aralkenyl radicals are "higher aralkenyl" radicals having aryl radicals attached to alkenyl radicals having seven to fifteen carbon atoms. The aryl in said aralkenyl may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and tert-butoxy. The "alkoxy" radicals may be

further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The aryl in said aryloxy may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The aryl in said aralkoxy radicals may be additionally substituted with, for example halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phoxymethyl. The aryl in said aryloxyalkyl may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl. Also preferred alkoxyalkyl radicals are "higher alkoxyalkyl" radicals having seven to fifteen carbon atoms. An example of "higher alkoxyalkyl" is undecyloxymethyl.

The term "alkoxyalkenyl" embraces linear or branched alkenyl radicals having one or more alkoxy radicals attached to the alkenyl radical, that is, to form monoalkoxyalkenyl and dialkoxyalkenyl radicals. Preferred alkoxyalkenyl radicals are "lower alkoxyalkenyl" radicals having alkoxy radicals of six to fifteen carbon atoms. An examples of such radicals is -CH=CHOCH_3 . The "alkenyl" and/or "alkoxy" radicals may be

further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkenyl" and/or "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy,
5 trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aralkoxy" embraces alkoxy radicals having one or more aryl radicals attached to the alkoxy radical, that is, to form monoaralkoxy and diaralkoxy radicals. Preferred aralkoxy radicals are "lower aralkoxy" radicals
10 having alkoxy radicals of one to ten carbon atoms. Examples of such radicals include phenylmethoxy. The "aryl" and "alkoxy" radicals may be further substituted with, for example, halogen, alkyl, haloalkyl, alkoxy, nitro, carboxy, carbalkoxy, alkylthio, alkylamino,
15 dialkylamino, and amino. Examples of such radicals include, for example, methyl, chloro, trifluoromethyl, methoxy, $-CO_2H$, $-CO_2C_2H_5$, methylthio, methylamino and dimethylamino.

The term "heteroaralkoxy" embraces alkoxy radicals
20 having one or more heteroaryl radicals attached to the alkoxy radical, that is, to form monoheteroaralkoxy and diheteroaralkoxy radicals. Preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having alkoxy radicals of one to ten carbon atoms. Examples of
25 such radicals include oxaranylmethoxy and 2-pyridylmethoxy. The "heteroaryl" and "alkoxy" radicals may be further substituted with, for example, halogen, alkyl, haloalkyl, alkoxy, nitro, carboxy, carbalkoxy, alkylthio, alkylamino, dialkylamino, and amino. Examples
30 of such radicals include, for example, methyl, chloro, trifluoromethyl, methoxy, $-CO_2H$, $-CO_2C_2H_5$, methylthio, methylamino and dimethylamino.

The term "carbonyl" embraces the $-C(O)-$ radical found in such compounds as aldehydes and ketones.

35 The term "alkoxycarbonyl" embraces a carbonyl group, as defined above, having an attached alkoxy radical.

Examples of such radicals include methoxycarbonyl and ethoxycarbonyl. The "alkoxy" radicals may be further substituted with, for example, halogen and cyano.

Examples of such radicals include fluoroethoxycarbonyl and cyanomethoxycarbonyl.

The term "arylcarbonyloxy" embraces a carbonyl radical attached through an oxygen atom to other radicals and additionally having an aryl radical attached to the carbonyl group. More preferred arylcarbonyloxy radicals are "lower arylcarbonyloxy" radicals having phenyl radicals attached to the carbonyl radical as described above, such as benzoyloxy. The aryl in said arylcarbonyloxy radicals may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "arylcarbonyloxyalkyl" embraces an arylcarbonyloxy radical, as defined above, attached to an alkyl radical. More preferred arylcarbonyloxyalkyl radicals are "lower arylcarbonyloxyalkyl" radicals wherein the aryl portion of the arylcarbonyloxyalkyl radical comprises one or more phenyl radicals attached to the carbonyl as described above, such as benzoyloxymethyl. The aryl in said arylcarbonyloxy radicals may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "thio" embraces radicals containing a divalent sulfur. An example of a thio radical is the sulfhydryl (or -SH) radical.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. Examples of "lower alkylthio" include methylthio (-S-CH₃) and ethylthio (-S-CH₂CH₃). Also preferred alkylthio radicals are "higher alkylthio" radicals having seven to fifteen carbon atoms. An

example of "higher alkylthio" is dodecylthio.

The term "cycloalkylthio" embraces radicals containing a cyclic alkyl radical, of three to ten carbon atoms, attached to a divalent sulfur atom. More preferred
5 cycloalkylthio radicals are "lower cycloalkylthio" radicals having three to six carbon atoms. An example of "lower cycloalkylthio" is cyclobutylthio. Also preferred cycloalkylthio radicals are "higher cycloalkylthio" radicals having seven to fifteen carbon atoms. An
10 example of "higher cycloalkylthio" is cyclooctylthio.

The term "arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio. The aryl in said arylthio may be additionally substituted with, for
15 example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "heteroarylthio" embraces heteroaryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include pyridylthio. The heteroaryl in said heteroarylthio may be additionally
20 substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl and
25 ethylthioethyl. Also preferred alkylthioalkyl radicals are "higher alkylthioalkyl" radicals having seven to fifteen carbon atoms. An example of "higher alkylthioalkyl" is undecylthiomethyl.

The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl. The aryl in said arylthioalkyl may be additionally substituted with
30 halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "heteroarylthioalkyl" embraces heteroarylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include
35

pyrimidinylthiomethyl. The heteroaryl in said heteroarylthioalkyl may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

- 5 The term "halo" or "halogen" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, 10 dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may 15 have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl radicals include fluoromethyl, difluoromethyl, 20 trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "chlorinated methyl" means a 25 methyl group having one or more chlorine atoms bonded thereto, including a alkyl radical wherein all the hydrogen atoms are replaced by chlorine. The term "fluorinated alkyl" means an alkyl group having one or more fluorine atoms bonded thereto, including a methyl 30 radical wherein all the hydrogen atoms are replaced by fluorine. Fluorinated methyl is the preferred fluorinated alkyl. The term "chlorofluorinated methyl" means a methyl group having a chloro atom and one or two fluorine atoms bonded thereto, including a methyl radical 35 wherein all the hydrogen atoms are replaced by a chlorine atom and two fluorine atoms.

The term "amido" or "aminocarbonyl" embraces amino radicals attached to a carbonyl radicals. The amino radical in said amido radical may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkylamino" embraces an alkyl radical, as defined above, attached to an amino group. Examples of such alkylamino radicals include methylamino and ethylamino. The alkyl radical in said alkylamino radical may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "trialkylsilyl" embraces silyl radicals tri-substituted with alkyl radicals. Examples of such trialkylsilyl radicals include trimethylsilyl and triethylsilyl. The alkyl radical in said trialkylsilyl radical may be additionally substituted with, for example, halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

In addition to those substitutions described above, the substituents of the substituted alkyl, alkenyl, alkynyl, aryl, and heteroaryl groups and other moieties described above include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, nitrogen, oxygen, sulfur, haloalkyl such as trifluoromethyl, lower alkoxy such as methoxy, ethoxy or butoxy, lower haloalkoxy, hydroxy, halogen such as chloro or fluoro, nitro, amino, and keto.

As used herein, "Ph" means phenyl; "Me" means methyl; "Et" means ethyl; "Ethylidene" means the group $\text{CH}_2\text{CH=}$; "R" means alkyl unless otherwise defined; "Pr" means propyl; "i-Pr" means iso-propyl; "i-propoxy" means isopropoxy; "c-Pr" means cyclopropyl; "Bu" means butyl;

"i-Bu" means iso-butyl; "t-Bu" means tert-butyl; "c-Bu" means cyclobutyl; "Hx" means hexyl; "c-C₅H₉" means cyclopentyl; "c-Hx" means cyclohexyl; "B" means boron; "Br" means bromine; "C" means carbon; "Cl" means chlorine; "F" means fluorine; "H" means hydrogen; "I" means iodine; "N" means nitrogen; "O" means oxygen; "P" means phosphorus; "S" means sulfur; "Si" means silicon; and "TBS" means dimethyl-tert-butyl-silyl.

10 Preparation of Substituted Pyridines

A number of the substituted pyridine compounds and intermediates having pharmacological activity were previously known as herbicides. Accordingly, the specific and/or general procedures for preparing such known compounds can be found in U.S. Patents 4,609,399, 4,655,816; 4,692,184; 4,698,093; 4,789,395; 4,885,026; 4,936,905; 4,988,384; 5,037,469; 5,125,961; 5,129,943; 5,156,670; 5,169,432; and 5,260,262; and in Chem. Pharm. Bull., 14, 918 (1966); Biokhimiya, 33, 350 (1968); J. Agric Chem., 39, 2072 (1991); Ann., 246, 32 (1888); Res. Discl., 295, 867 (1988); and J. Heterocyclic Chem., 26, 1771 (1989). These references are incorporated herein by reference.

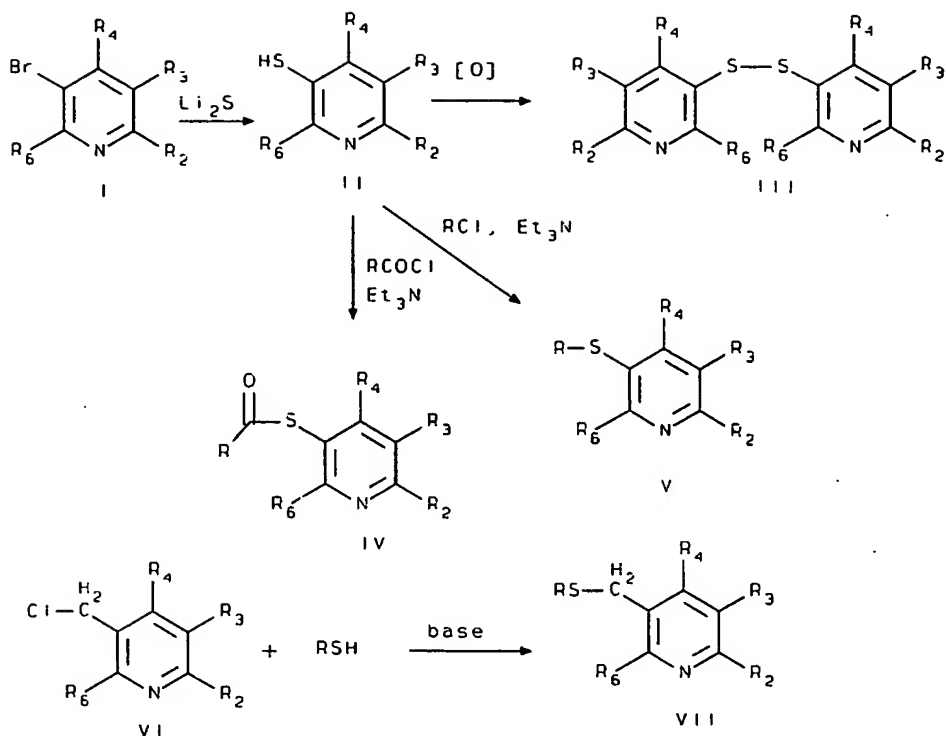
The "Procedure Reference" column of Tables 1-2 provides exemplary references disclosing the specific procedures for the preparation of many of the substituted pyridines identified in those Tables. These references are incorporated herein by reference. One skilled in the art can prepare these compounds based on the disclosure of the references. A reference to "See Example ____" indicates that the procedure, while not specifically for the preparation of the compound listed in the Table, is sufficiently analogous that one skilled in the art can prepare the compound by making the necessary modifications to the referenced procedure without undue experimentation. Additional information for the

preparation of a number of these compounds also is set forth below. A written description of the procedures for preparing the remaining substituted pyridines for which no corresponding reference appears in the Tables is set
5 forth below.

 The 2,6-dimethyl- and 2,6-bis(methoxymethyl)-3,5-pyridinedicarboxylates (such as Compound 92 and Compound 106) can be prepared by the procedure described in Ann., 246, 32 (1888) and Ann., 241, 1 (1882).

10 The 5-mercapto analogs II (see, e.g., Example 2 below) can be prepared from the 5-bromo derivative I (which itself can be prepared as shown in U.S. Patent 4,789,395) by reaction with lithium sulfide. The 5-mercapto analogs II can be converted to the disulfide
15 III by oxidation or by reaction with a mixture of 2-fluoroethanol, methanesulfonyl chloride and triethylamine or by reaction with bromine in acetic acid. The 5-mercapto analogs can be reacted with alkyl halides and acyl halides to give the derivatives IV and V cited
20 in this invention. Alternatively pyridyl methylchloride VI can be reacted with a thiol to give the sulfide VII (see, e.g., Example 22 below)

185

**Example 1**

Preparation of Methyl 2-(Difluoromethyl)-5-mercapto-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate (Compound 7)

To a stirred solution of 10.11 g (0.026 mol) of methyl 5-bromo-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 122 of U.S. patent 5,019,153) in 75 mL dry DMF was added 1.42 g

186

- (0.031 mol) of lithium sulfide in one portion and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with 150 mL of 10% HCl solution and extracted with ether (3x100 mL). The combined extracts were washed with water, dried (MgSO₄) and evaporated. The residue was purified by kugelrohr distillation (oven temperature 100-110 °C, 1.5 torr) to give 7.35 g (83%) of product as a yellow-green oil:
- Anal. Calcd. for C₁₃H₁₄F₅NO₂S: C, 45.48; H, 4.11; N, 4.08
Found: C, 45.58; H, 4.14; N, 4.08.

Example 2

- Preparation of Dimethyl 5,5'-Dithiobis[2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate] (Compound 181)

- To a solution of 1.14 g (0.018 mol) of 2-fluoroethanol and 0.95 g (0.0094 mol) of triethylamine in 20 mL dry THF at -78 °C was added 1.07 g (0.0094 mol) of methanesulfonyl chloride in 10 mL of dry THF. After stirring the mixture for 30 min, 2.5 g (0.0073 mol) of product of example 1 and 0.95 g (0.0094 mol) of triethylamine were added. The mixture was slowly warmed to room temperature and stirred for an additional 2 h. The reaction mixture was evaporated, the residue was diluted with 100 mL of water and extracted with 125 mL of ether. The organic layer was washed with water, dried (MgSO₄) and evaporated. The residue was purified by preparative HPLC (8% ethyl acetate-hexane) to give 1.82 g (73%) of product as a yellow oil:

- Anal. Calcd. for C₂₆H₂₆F₁₀N₂O₄S₂: C, 45.61; H, 3.83; N, 4.09
Found: C, 45.80; H, 3.87; N, 4.02

- The same compound can be obtained by reacting compound 7

(see Table 1) with one half equivalent of bromine in acetic acid.

Example 3

- 5 Preparation of Methyl 5-(4-t-Butylphenylthiomethyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 3)

Reaction of methyl 5-chloromethyl-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 3 of U.S. patent 5,169,432) with 4-t-butylbenzenethiol according to the procedure of example 29 of U.S. patent 5,169,432 yielded the product as an oil.

15

Anal. Calcd. for $C_{18}H_{20}F_5NO_3$: C, 54.96; H, 5.13; N, 3.56.
Found: C, 55.05; H, 5.13; N, 3.51

Example 4

- 20 Preparation of Ethyl 2,6-Bis(trifluoromethyl)-4-[4-(isopropylphenyl)thio]-5-methyl-3-pyridinecarboxylate (Compound 11)

Reaction of ethyl 2,6-bis(trifluoromethyl)-4-chloro-5-methyl-3-pyridinecarboxylate (example 65 of U.S. patent 4,655,816) with 4-isopropylbenzenethiol according to the procedure in example 23 of U.S. patent 4,655,816) yielded the desired product.

30

Example 5

Preparation of Ethyl 2,6-Bis(trifluoromethyl)-4-(isopropoxy)-5-methyl-3-pyridinecarboxylate (Compound 53)

- 35 Example 37 of U.S. patent 4,655,816 discloses a procedure for the preparation of this compound.

Example 6

Preparation of Methyl 2,6-bis(Trifluoromethyl)-4-(benzyloxy)-3-pyridinecarboxylate (Compound 37)

- 5 Example 9 of U.S. patent 4,655,816 discloses a procedure for the preparation of this compound.

Example 7

- 10 Preparation of Methyl 2,6-Bis(trifluoromethyl)-5-(4,5-dihydro-2-thiazolyl)-4-(2-methylpropyl)-3-pyridinecarboxylate (Compound 12)

- 15 Example 21 of U.S. Patent 4,988,384 discloses a procedure for the preparation of this compound.

Example 8

Preparation of Diethyl 2,6-Bis(trifluoromethyl)-4-(2-methylpropyl)-3,5-pyridinedicarboxylate (Compound 36)

- 20 Example 7 of U.S. Patent 4,692,184 discloses a procedure for the preparation of this compound.

Example 9

- 25 Preparation of Di-t-Butyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridine-dicarboxylate (Compound 9)

- 30 Reaction of the product of step 6 of U.S. patent 4,988,384 with excess t-butanol according to the procedure of example 56 of U.S. patent 4,692,184 yielded the product, mp 48-50 °C.

Example 10

Preparation of Methyl 2-(difluoromethyl)-5-(1-hydroxyl-furylmethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 13)

5

Reaction of methyl 2-(difluoromethyl)-5-formyl-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (compound B1 of U.S. Patent 5,169,432) with 2-furyllithium according to the procedure in Example H of U.S. patent 5,260,262 yielded the product as an orange oil, n_D^{25} 1.4863.

10

Example 11

Preparation of Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[(methoxycarbonyl)thio]-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 6)

15

To a stirred solution of 3.05 g (0.0089 mol) of product of example 1 and 0.094 g (0.01 mol) of methyl chloroformate in 25 mL dry THF was added 1.16 g (0.012 mol) of triethylamine dropwise at room temperature. After stirring for 30 min, the solvent was evaporated under reduced pressure. The residue was diluted with 100 mL of water and extracted with ether (3x50 mL). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. Purification of the residue by preparative HPLC (5% ethyl acetate-hexane) gave 2.75 g (77%) of product as a yellow oil: n_D^{25} 1.5830.

20

25

Anal. Calcd. for $C_{15}H_{16}F_5NO_4S$: C, 44.89; H, 4.02; N, 3.49
Found: C, 44.97; H, 4.04; N, 3.47

30

Example 12

Preparation of Methyl

2-(Difluoromethyl)-5-[(i-propylthio)
carbonyl]-4-(cyclobutyl)-6-(trifluoromethyl)-3-
5 pyridinecarboxylate (Compound 14)

Methyl 5-chlorocarbonyl-4-cyclobutyl-2-(difluoromethyl)
-6-(trifluoromethyl)-3-pyridinecarboxylate prepared
similarly to the procedure in step 7 of U.S. patent
10 4,988,384 was reacted with 2-propanthiol according to the
procedure in example 141 of U.S. patent 4,692,184 to give
the product as an oil, n_D^{25} 1.4946.

Anal. Calcd. for $C_{17}H_{18}F_5NO_3S$: C, 49.63; H, 4.41; N, 3.40;
15 S, 7.79.

Found: C, 49.19; H, 4.59; N, 3.19; S, 7.40

Example 13

Preparation of Methyl 2,6-Bis(trifluoromethyl)-4-
20 (diphenylaminocarbonyloxy)-3-pyridinecarboxylate
(Compound 25)

To a solution of 2 g (0.0069 mol) of methyl
2,6-bis(trifluoromethyl)-4-hydroxy-3-pyridinecarboxylate
25 (example 4 of U.S. patent 4,655,816) in 20 mL of
acetonitrile was added 0.7 g of triethylamine. A solution
of 1.6 g (0.0069 mol) of diphenylcarbonyl chloride in 20
mL of acetonitrile was added to the above mixture and the
resulting mixture was stirred at room temperature over
30 the weekend. The precipitate formed was filtered off and
the filtrate was concentrated in vacuo. The residue was
slurried with ether. The insoluble material was filtered.
The ether filtrate was concentrated and the residue was
recrystallized from cyclohexane to give a white solid, mp
35 114-116 °C.

191

Anal. Calcd. for $C_{22}H_{14}F_6N_2O_4$: C, 54.55; H, 2.91; N, 5.78.
Found: C, 54.69; H, 3.05; N, 5.69.

Example 14

- 5 Preparation of 3-Methyl 5-Ethyl 2-(Difluoromethyl)-4-
mercapto-6-(trifluoromethyl)-3,5-pyridinedicarboxylate
(Compound 2)

To a 5 °C solution of 6 g (0.017 mol) of 3-ethyl 5-methyl
10 6-(difluoromethyl)-4-chloro-2-(trifluoromethyl)-3,5-
pyridinedicarboxylate (example 103 of U.S. patent
4,698,093) in 50 mL of dry THF was added 1.6 g (0.022
mol) of KSH. The resulting mixture was stirred at 0 °C for
15 min then at room temperature for 16 h. The mixture was
poured into 5 % NaOH and extracted with ether. The
aqueous layer was made acidic with concentrated HCl and
the product was extracted into ethyl acetate. The ethyl
acetate layer was dried ($MgSO_4$) and solvent removed in
vacuo affording 4.64 g of a light yellow oil.
20 Purification by HPLC (10% MeOH/5% ethyl acetate/85%
cyclohexane) gave 3.25 g of a yellow oil, n_D^{25} 1.4775.

Anal. Calcd. for $C_{12}H_{10}F_5NO_4S$: C, 40.12; H, 2.81; N, 3.90;
S, 8.92.
25 Found: C, 40.20; H, 2.79; N, 3.86; S, 8.90

Example 15

- Preparation of Diethyl
2-(Difluoromethyl)-4-(t-butylthio)-6-(trifluoro-
30 methyl)-3,5-pyridine-dicarboxylate (Compound 39)

Example 108 of U.S. patent 4,698,093 discloses a
procedure for the preparation of this compound.

Example 16

Preparation of Diethyl 2-(Difluoromethyl)-4-(cyclopentylthio)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (Compound 22)

5

Example 109 of U.S. patent 4,698,093 discloses a procedure for the preparation of this compound.

Example 17

10 Preparation of Methyl 5-Chloromethyl-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 83)

15 Example 3 of U.S. patent 5,169,432 discloses a procedure for the preparation of this compound.

Example 18

20 Preparation of Methyl 2-(Difluoromethyl)-5-(1,3-dioxan-2-yl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 59)

Example 109 of U.S. patent 4,988,384 discloses a procedure for the preparation of this compound.

25

Example 19

Preparation of Methyl 2-(Difluoromethyl)-5-(methylthiomethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 60)

30 Example 47 of U.S. patent 5,169,432 discloses a procedure for the preparation of this compound.

Example 20

Preparation of Dimethyl 2-(Difluoromethyl)-4-{[(2-methylthio)pyrimidin-4-yl]methyl}-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (Compound 67)

5

To a solution of 7.1 g (0.021 mol) of dimethyl 2-(difluoromethyl)-4-methyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (example 218 of U.S. Patent 4,692,184) in 90 mL of anhydrous THF cooled to -30 °C under nitrogen was added 25 mL (0.025 mol) of 1.0 M lithium bis(trimethylsilyl)amide in THF controlling the temperature range at -20 °C to -30 °C. After 15 min at -30 °C a solution of 5.0 g (0.031 mol) of 4-chloro-2-methylthio-pyrimidine in 20 mL of THF was added. The mixture is allowed to warm to -10 °C, where it was held for 1.5 h. The reaction mixture was added to diluted HCl and worked up with methylene chloride. The product was purified by HPLC (12% ethyl acetate in hexane), and by recrystallization from hexane to give amber-yellow solid, mp 89-91 °C.

15

20

Anal. Calcd. for $C_{17}H_{14}F_3N_3O_4S$: C, 45.24; H, 3.13; N, 9.31. Found: C, 45.27; H, 3.15; N, 9.26.

25

Example 21

Preparation of Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-5-[(trimethylsilyl)ethynyl]-3-pyridinedicarboxylate (Compound 19)

30

35

A mixture of 6 g (0.015 mol) of methyl 5-bromo-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 122 of U.S. patent 5,019,153), 0.1 g of palladium (II) acetate, 0.2 g of triphenylphosphine, 30 ml of triethylamine and 5 g of (trimethylsilyl)acetylene was held at reflux under nitrogen for 4 hours and cooled to room temperature. The

194

reaction mixture was filtered through a small plug of celite and the filtrate was concentrated in vacuo to give a dark oil. The residue was Kugelrohr distilled to give 5 g of light brown oil. which was purified by Chromatotron (9:1 cyclohexane/ methylene chloride). A total of 3 g (48% yield) of a yellow oil (n_D^{25} 1.4681).

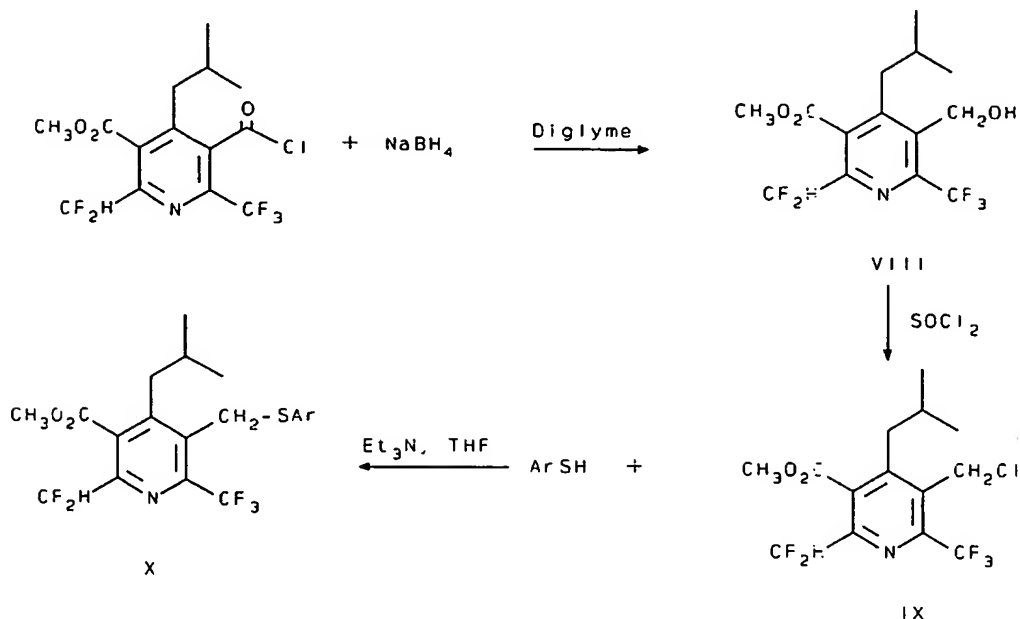
The 5-arylthiomethyl- and 5-heteroarylthiomethyl-pyridines shown in Table 6 can be prepared by reaction of an arylthiol or a heteroarylthiol with substituted 5-pyridylmethyl halide in the presence of base similar to the procedure in Example 3. The following procedures describe a typical synthesis of these compounds.

15

195

Scheme 1

Synthesis of Aryl Pyridylmethyl Sulfides X



General Procedure for the Preparations of Sulfides X from

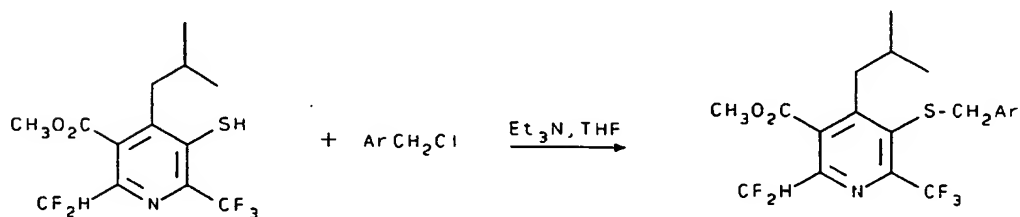
5 IX.

To a solution of 1 mmol of triethylamine in 50 mL of THF was added 1 mmol of an arylthiol or a heteroarylthiol and 1 mmol of IX. The reaction mixture was stirred overnight and filtered to remove triethylamine hydrochloride. The filtrate was diluted with 50 mL of ether and washed with water. The ether layer was dried (MgSO_4) and concentrated in rotovap to give the product.

The 5-aryl- and heteroaryl-methylthiopyridines shown in Table 7 can be prepared by reaction of compound 7 with the appropriate arylmethyl chloride or heteroarylmethyl chloride.

5

Scheme 2
Synthesis of Arylmethyl Pyridyl Sulfides XI



10 Compound 7

XI

General Procedure for the Preparations of Sulfides XI

To a solution of 1 mmol of arylmethyl chloride and 1 mmol of methyl 2-(difluoromethyl)-4-isobutyl-5-mercapto-6-(trifluoromethyl)-3-pyridinecarboxylate (compound 7) in 50 mL of DMF was added 1 mmol of triethylamine. The reaction mixture was stirred until TLC showed that the reaction was mostly complete. The reaction mixture was diluted with ethyl acetate and washed successively with 1 N KHSO₄, water, 10% sodium hydroxide (to remove unreacted methyl 2-(difluoromethyl)-4-isobutyl-5-mercapto-6-(trifluoromethyl)-3-pyridinecarboxylate) and brine, dried (Na₂SO₄) and concentrated in rotovap. If necessary, the residue was purified by HPLC or chromatotron.

Example 22

Preparation of Methyl 5-{[3-(Carbomethoxy)-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-5-pyridyl]thiomethyl}-2-(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 182)

To a solution of 550 mg (1.53 mmol) of 5-chloromethyl-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 3 of U.S. patent 5,169,432) and 524 mg (1.53 mmol) of methyl 2-(difluoromethyl)-4-isobutyl-5-mercapto-6-(trifluoromethyl)-3-pyridinecarboxylate (compound 7) in 50 mL of DMF was added 154 mg (1.53 mmol) of triethylamine. The reaction mixture was stirred for 40 h, diluted with ethyl acetate (400 mL) and washed successively with 1 N KHSO₄ (200 mL) and brine (100 mL), dried (Na₂SO₄), and concentrated in a rotovap. The residue was purified by flash chromatography (10% EtOAc-hexane) to give 550 mg of material. TLC showed that this material contained product, compound 7 and disulfide of compound 181. A 110 mg of this material was further purified by HPLC (0-40% EtOAc-Hexane) to give pure product.

Reaction of compound 7 with the appropriate alkyl halide or acid chloride in THF in the presence of one equivalent of triethylamine with the procedure similar to Example 22 and Example 6 gave compounds 5, 33, 44, 145, 146, 147, and 183. Compound 148 was isolated as a byproduct from Example 2. The following example describes a typical procedure for the synthesis of these compounds.

Example 23

Preparation of Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 5)

5

To a solution of 0.5 g of palmitoylchloride in 50 ml of THF was added 0.62 g of compound 7 followed by 0.37 g of triethylamine. The reaction mixture was stirred for 1 h, poured into water and extracted with ether. The ether
10 extract was dried over MgSO_4 and concentrated in vacuo to give the product.

The compounds in Table 3 and Table 4 are prepared from reaction of methyl 5-chlorocarbonyl-2-(difluoromethyl)-4-
15 (2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (product of step 7 in US 4,988,384) with appropriate the phenols and thiophenols. The following example describes a typical procedure for the synthesis of these compounds.

20

Example 24

Preparation of Methyl 2-(Difluoromethyl)-5-[(2,4-dimethyl-phenyl)thio]carbonyl}-4-(2-methylpropyl)-
25 6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 158)

To a solution of 1 g of 2,4-dimethylbenzenethiol and 3.29 g of methyl 5-chlorocarbonyl-2-(difluoromethyl)-4-2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate
30 in 50 ml of THF was added 0.81 g of potassium t-butoxide. The reaction mixture was stirred for 1 h and poured into ice-water. The organic was extracted into methylene chloride. The methylene chloride extract was dried over MgSO_4 and concentrated in vacuo. The residue was
35 recrystallized from ether-hexane to give 2.73 g of the product.

The unsymmetric aryl pyridyl disulfides can be prepared by oxidation of a mixture of the appropriate pyridinethiol and arylthiol with bromine in acetic acid followed by separation of the unsymmetric aryl pyridyl disulfide from the symmetric diaryl disulfide and dipyridyl disulfide by chromatography. The following example describes a typical procedure for the synthesis of these compounds.

10 Example 25

Preparation of Methyl 5-(4-t-Butylphenyldithio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 180)

15 To a mixture of 100 mg of compound 7 and 48.6 mg of
4-t-butylbenzenethiol in 5 ml of acetic acid was added 23
mg of bromine. The reaction mixture was stirred for 1 h,
poured into water and extracted with ether. The ether
extract was washed with saturated sodium bicarbonate,
20 dried over MgSO_4 and concentrated in vacuo. The residue
was purified by preparative TLC (9:1 Hexane: EtOAc) on
silica gel to give the desired product.

Example 26

25 Preparation of Dimethyl 2,6-Bis(trifluoromethyl)-4-(trimethylsilyl)-3,5-pyridinedicarboxylate
(Compound 31)

To 10 ml of dry THF at -78 °C was added 8.4 ml (0.012 mol) of 1.55 M n-butyllithium in hexane followed by 1.21 g (1.7 ml, 0.012 mol) of diisopropylamine. After stirring at -78 °C for 30 min, a solution of 3.59 g (0.01 mol) of diethyl 2,6-bis(trifluoromethyl)-3,5-pyridine-dicarboxylate (prepared by the procedure similar to example 1 of U.S. patent 4,692,184) in 10 ml of dry THF was added. The reaction turned dark red and after

200

stirring at -78 °C for 10 min, 4.4 g (0.05 mol) of chlorotrimethylsilane was added. The reaction was warmed to room temperature, stirred for 30 min and then was poured into 0 °C water, extracted with ether, dried (MgSO₄) and concentrated in vacuo. The residue was purified by HPLC (1:20 EtOAc:hexane) affording 2.09 g of the product as a light yellow oil which crystallized upon standing: mp 29-31 °C.

10

Example 27

Preparation of Diethyl 5,5'-(Carbonyldiimino)bis [6-(difluoromethyl)-4-ethyl-2-(trifluoromethyl)-3-pyridinecarboxylate (Compound 48)

15 A mixture of 2-(difluoromethyl)-5-ethoxycarbonyl-4-ethyl-(6-trifluoromethyl)-3-pyridinecarboxylic acid (example 28 of U.S. patent 4,692,184) and 40 ml of thionyl chloride was held at reflux for 1 h and concentrated in vacuo. The residue was dissolved in 50 ml of toluene and treated with 20 g of sodium azide and 0.1 g of 18-crown-6 (Aldrich). The reaction mixture was held at reflux for 24 h and filtered. The filtrate was treated with 50 ml of concentrated HCl and stirred for 18 h. The reaction mixture was treated with 50 ml of water and the toluene layer was separated and concentrated in vacuo. The residue was treated with 40 ml of trifluoroacetic acid and 10 ml of water then was held at reflux for 30 min and concentrated in vacuo. The residue was stirred with water and extracted with ether. The ether layer was washed with saturated sodium bicarbonate, dried (MgSO₄) and concentrated in vacuo to give 7.9 g of syrup. This syrup was stirred with ether and filtered to give 0.58 g of product, mp 219-221 °C.

35

Example 28

Preparation of Dimethyl 5,5'-Carbonylbis[4-(1-methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate (Compound 54)]

5

Step 1: Methyl 4-Hydroxy-2-(trifluoromethyl)-3-pyridinecarboxylate.

A mixture of 105 g (0.5 mol) of methyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenate (example 2 of U. S. patent 10 4,655,816), acetic anhydride (152 g), and trimethyl orthoformate (106 g) was held at reflux for 16 h then distilled to remove low boiling material (bp 65-90 °C). The remaining material was concentrated in vacuo and the residue was kugelrohr distilled at 2 torr (80-120 °C) to 15 give 114 g of distillate. This distillate (44 g) was added dropwise to a mixture of 14.5 g of 60% sodium hydride oil dispersion in 100 ml of 1,2-dimethoxyethane (DME). The reaction mixture was maintained at 25-30 °C with an ice-water bath. The reaction mixture was stirred 20 at room temperature for 18 h and poured into 300 ml of ice-water. The aqueous layer was extracted with ether and filtered. The aqueous layer was acidified with concentrated HCl. The oil precipitate was extracted into ether. The ether extract was extracted with 10% potassium 25 carbonate. The potassium carbonate layer was acidified with concentrated HCl. The precipitate was filtered and air dried to give 20.4 g of the product, mp 78-82 °C.

Step 2: Methyl 4-(1-Methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate (Compound 127). 30

A mixture of 7.0 g of product of step 1, 4.74 g of potassium carbonate, 14 g of 2-iodopropane and 50 ml of acetone was held at reflux for 18 h and concentrated in 35 vacuo. The residue was treated with water and extracted with ether. The ether extract was dried (MgSO₄) and

202

concentrated in vacuo. The residue was crystallized from hexane at low temperature to give 6.2 g of solid, mp 57.5-58.5 °C.

Compound 121 in Table 1 was similarly prepared except using ethyl 2-acetyl-3-amino-4,4,4-trifluorobutenoate (example 1 of U.S. Patent 4,655,816) as the starting material in step 1.

Step 3: Dimethyl 5,5'-Carbonylbis[4-(1-methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate, Compound 54.

To a cold (-78 °C) solution of 20 ml dry DME was added 11.5 ml of 1.6 M butyllithium in hexane followed by 2.5 ml of diisopropylamine. The reaction mixture was stirred for 10 min. To the above solution was added a solution of 4.2 g of product of step 2 in 15 ml of dry DME. The reaction mixture turned orange. After 5 min stirring, 3.3 ml of ethyl chloroformate was added to the reaction mixture. After 10 min stirring, the reaction mixture was poured into water and extracted with ether. The ether extract was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to give 3.45 g of oil which was crystallized from hexane to give 2.2 g of solid, mp 74-75 °C.

Example 29

Preparation of Methyl 2-(Difluoromethyl)-4-cyclobutyl-5-(1-pyrrolyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 70)

A solution of 1.62 g (5 mmol) of methyl 5-amino-2-(difluoromethyl)-4-cyclobutyl-6-(trifluoromethyl)-3-pyridinecarboxylate (example A-2 of U.S. patent 5,114,465) and 0.8 g (6 mmol) of 2,5-dimethoxytetrahydrofuran in 10 ml of acetic acid as heated at 70 °C

for 2.5 h. The reaction mixture was then diluted with 100 ml of water and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate (3x 100ml), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% EtOAc in hexane) to give the product, mp 70-71 °C.

Example 30

10 Preparation of Methyl 2-(Difluoromethyl)-4-(2-methyl-propyl)-5-(aminothionocarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 77)

To 16.5 g of methyl 6-(difluoromethyl)-4-(2-methylpropyl)-5-(methoxycarbonyl)-2-(trifluoromethyl)-a-oxo-3-pyridineacetate (prepared by example E of U.S. patent 5,298,479) in 60 ml of methylene chloride was added 25 ml of concentrated ammonium hydroxide. The reaction mixture was stirred for 2 h and the aqueous layer was saturated with NaCl and the organic was extracted into methylene chloride. The methylene chloride layer was dried (MgSO₄) and concentrated in vacuo. The residue was recrystallized from 20% EtOAc-benzene to give 12.5 g of 6-(difluoromethyl)-4-(2-methylpropyl)-5-(methoxycarbonyl)-2-(trifluoromethyl)-a-oxo-3-pyridineacetamide. A mixture of 2.4 g of this material, 2.0 g of phosphorus pentasulfide, 2 g of Celite and 16 ml of toluene was held at reflux for 2h. The mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to give an oil which crystallized from 3% EtOAc in hexane as a solid.

Example 31

Preparation of Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[(tetrahydro-2-furyl)thio]-6-(trifluoromethyl)-3-pyridinecarboxylate

5 (Compound 150)

A mixture of 7.07 g (0.021 mol) of compound 7, 2.92 g (0.042 mol) of dihydrofuran, and catalytic toluenesulfonic acid (9 mg) in 80 ml of ether was stirred
10 overnight. The reaction mixture was concentrated in vacuo, and the residue was purified by HPLC (20% EtOAc in hexane) to give 5.82 g (68%) of the desired product as a yellow oil, n_D^{25} 1.5803.

15

Example 32

Preparation of Dimethyl 2,6-Bis(methoxymethyl)-4-propyl-3,5-pyridinedicarboxylate (Compound 92)

A solution of 4.93 g (0.068 mol) of n-butyraldehyde, 20 g
20 (0.137 mol) of methyl 4-methoxyacetoacetate, 15 ml of ethanol, and 6.8 ml of concentrated ammonium hydroxide was held at reflux for 5 h and poured into 200 ml of ice water. The oil which precipitated out was extracted into ether. The ether layer was washed with water, dried
25 (MgSO₄), and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc in hexane) to give 7.91 g of yellow solid. Recrystallization from hexane gave 6.44 g of dimethyl 2,6-bis(methoxymethyl)-1,4-dihydro-4-propyl-3,5-pyridinedicarboxylate as yellow solid. A
30 solution of this solid (4.35 g, 0.0133 mol) in 75 ml of 70% acetic acid was heated to 70 °C. Chromium trioxide (3.99 g, 0.0399 mol) was added slowly. The reaction mixture was stirred at 65-70 °C for 1 h and poured into ice water and extracted with ether. The combined ether
35 layers were stirred with 500 ml of saturated sodium bicarbonate. The ether layer was dried (MgSO₄) and

concentrated in vacuo. The residue was kugelrohr distilled at 140 °C at 1 torr to give an oil, n_D^{25} 1.4924.

Example 33

- 5 Preparation of Methyl 5-[(Diethoxyphosphinyl)carbonyl]-2-(difluoromethyl)-4-(1-methylethylamino)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 85)

A mixture of 46.27 g (0.1 mol) of 3-methyl 5-benzyl
10 2-(difluoromethyl)-4-(1-methylethylamino)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (example 181 of U.S. patent 4,698,093) in 1.2 L of a 1:5 mixture of THF in methanol was hydrogenated using catalytic 5% Pd/C under 50 lb of hydrogen pressure for 48 h. The reaction mixture
15 was filtered through Celite and concentrated in vacuo to give 36 g of 3-methyl 5-hydrogen 2-(difluoromethyl)-4-(1-methylethylamino)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate. To a mixture of 34.7 g of this monoacid in 400 ml of carbon tetrachloride was added 23 g
20 (0.11 mol) of phosphorus pentachloride. The reaction mixture was stirred at room temperature until HCl evolution stopped. The reaction mixture was held at reflux for 20 min and concentrated in vacuo affording 38.04 g of monoacid chloride as a yellow oil. A portion
25 (3.75 g 0.01 mol) of this oil and 1.7 g (0.01 mol) of triethyl phosphite was heated to 160 °C and then cooled. The resulting oil was purified by HPLC (25% EtOAc in hexane) affording 2.09 g of (44%) of product as a thick yellow oil.

30

Example 34

Preparation of Methyl 2-(Difluoromethyl)-5-{[methoxy (methylthio)methylene]amino}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 27)

35

To a solution of 2.5 g (6.8 mmol) of methyl

2-(difluoromethyl)-5-isothiocyanato-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (U.S. patent 5129943 example 41 step A) in 25 ml of anhydrous THF at room temperature was added 1.6 g (7.5 mmol) of 25% sodium methoxide in methanol. The reaction mixture was stirred for 30 min and was treated with 1.93 g (14 mmol) of methyl iodide. The reaction mixture was stirred for 3 h and concentrated in vacuo. The residue was partitioned with ether (75 ml) and 10% HCl (50 ml). The organic layer was washed with water (3x 30 ml), dried (MgSO₄), and concentrated in vacuo. The crude product was purified by chromatotron (20% EtOAc in hexane) to afford 2.32 g (82%) of a colorless oil, n²⁵D 1.5982.

Example 35

Preparation of Methyl 5-{[Bis(methylthio)methylene]amino}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 42)

This was prepared similar to example 33 except sodium methanethiolate was used instead of sodium methoxide. The product was isolated as a colorless oil, n²⁵D 1.5850.

Example 36

Preparation of Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(oxiranylmethoxy)methylene]amino}-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 30)

A slurry of 10.0 g (0.028 mol) of methyl 2-(difluoromethyl)-5-formylamino-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (U.S. patent 5,037,469 example G1) and 6.03 g (0.029 mol) of phosphorus pentachloride in 75 ml of CCl₄ was stirred overnight at room temperature. The solvent was evaporated to give crude imidoyl chloride.

207

To a stirred solution of 6.02 g (0.0163 mol) of the crude imidoyl chloride in 75 ml of anhydrous THF at room temperature was added 6.43 g (0.087 mol) of glycidol in one portion followed by 2.53 g (0.021 mol) of 4-dimethylaminopyridine. The reaction mixture was held at reflux for 3 h and concentrated in vacuo. The residue was partitioned with ether (100 ml) and water (50 ml). The organic layer was washed with 10% HCl (3 x 30 ml) and saturated sodium bicarbonate (3 x 30 ml), dried (MgSO₄), and concentrated in vacuo. The crude product was purified by chromatotron (20% EtOAc in hexane) to afford 2.58 g (38%) of a solid, mp 41-43 °C.

Example 37

Preparation of Methyl 2-(Difluoromethyl)-5-(iodomethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate (Compound 32)

Reaction of methyl 2-(difluoromethyl)-5-(chloromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate (U.S. patent 5,169,432 example 3) with sodium iodide in refluxing acetone according to the procedure known to those in the art yielded the product.

Compound 13 was prepared by the procedure in example H of U.S. patent 5,260,262. Compounds 89, 105, 131, and 133 were similarly prepared.

Compounds 34 and 40 were prepared from the 5-[(heteroaryl)hydroxymethyl] compounds which were prepared by the procedure H of U.S. patent 5,260,262. The following example described the preparations of these compounds.

35

Example 38

Preparation of Methyl 2-(Difluoromethyl)-5-[(methoxy)isothiazol-5-ylmethyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 34)

5 Methyl 2-(difluoromethyl)-5-[(isothiazol-5-yl)hydroxymethyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (prepared by the procedure similar to example H of U.S. patent 5,260,262) was alkylated with
10 methyl iodide by the procedure in example 61 of U.S. patent 5,169,432.

Example 39

Methyl 5-(Benzoyloxymethyl)-2-(difluoromethyl)-4-(cyclopropylmethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 41)

Reaction of methyl 2-(difluoromethyl)-5-(hydroxymethyl)-4-(cyclopropylmethyl)-6-(trifluoromethyl)-3-pyridine-
20 carboxylate (U.S. patent 5,169,432 example A compound A4) with. Benzoyl chloride and triethylamine according to the procedure in example 99 of U.S. patent 5,169,432 gave the product.

25 Example 40

Preparation of Methyl 2-(difluoromethyl)-5-[[isopropylimino(methylthio)methyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 58)

30 Reaction of methyl 5-chlorocarbonyl-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (step 7 of U.S. patent 4,988,384) with isopropylamine yielded the corresponding isopropylamide. A mixture of this amide (3.75 g), 1.97 g of PCl₅ and 150
35 ml of carbon tetrachloride was held at reflux overnight and concentrated in vacuo. The residue was dissolved in

60 ml of THF and cooled to 5 °C and treated with 0.27 g of sodium methanethiolate. The reaction mixture was stirred at room temperature overnight, poured into water and extracted into ether. The organic was dried (MgSO₄),
5 filtered, and concentrated in vacuo. The residue was purified by chromatotron (20% EtOAc in hexane) to give 1.0 g of pale yellow oil.

Compound 68 in Table 1 was similarly prepared except using methylamine instead of isopropylamine as a reagent.

10

Example 41

Preparation of 3-Ethyl 5-Isopropyl 4-hydroxy-2-(trifluoromethyl)-3,5-pyridinedicarboxylate
(Compound 101)

15 Ethyl 4-i-propoxy-2-(trifluoromethyl)-3- pyridine-carboxylate (prepared similar to step 2 of example 28) was reacted with 2 equivalents of lithium diisopropylamide as in step 3 of example 28 and quenched with dry ice instead of ethyl chloroformate. The reaction
20 mixture was stirred at -78 °C for 15 min then warmed to room temperature in 1 h. The reaction mixture was poured into water and extracted with ether. The aqueous layer was acidified with concentrated HCl to give 3-ethyl 5-hydrogen 4-isopropoxy-2-(trifluoromethyl)-3,
25 5-pyridinedicarboxylate as a solid, mp 97-99 °C. A mixture of 10 g of this acid and 25 ml of thionyl chloride was held at reflux for 1 h and concentrated. The residue was held at reflux with 15 ml of isopropanol for 1 h and concentrated. The residue was kugelrohr distilled at 0.15
30 torr to give product as an oil, n²⁵D 1.4620.

Compound 125 was similarly prepared except using ethanol instead of isopropanol as a reagent.

Example 42

Preparation of Methyl 4-(Cyclopropylmethyl)-2-(difluoromethyl)-5-(1-hydroxy-5-methyl-3-pyrrolidinyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 107)

5

To a solution of 16.5 g (68.3 mmol) of methyl 5-(1-cyano-3-butenyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 16 of U.S. patent 5,169,432) in 250 ml of ether cooled in an ice bath was added 91 ml (136 mmol) of diisobutylaluminum hydride (1.5 M in toluene). The reaction mixture was stirred on an ice bath for 30 min and was treated with 200 ml of 2.4 M HCl. The organic layer was washed with brine, dried (MgSO₄), and filtered through silica gel. The filtrate was concentrated in vacuo and the residue was purified by HPLC (17% EtOAc in hexane) to give 8.1 g of methyl 4-(cyclopropylmethyl)-2-(difluoromethyl)-5-(1-formyl-3-butenyl)-6-(trifluoromethyl)-3-pyridinecarboxylate.

20

To a solution of 5.8 g (14.8 mmol) of the above aldehyde in 100 ml of CCl₄ was added 1.1 g (15.8 mmol) of hydroxylamine hydrochloride. To the mixture was added 10 g of pyridine and the mixture was heated to reflux for 1.5 h. The reaction mixture was partitioned between ether and 2.4 M HCl. The organic layer was washed with brine, dried (MgSO₄), and filtered through silica gel, and the filtrate was concentrated in vacuo. The residue was purified by HPLC (15% EtOAc in hexane) to yield 1.6 g of the oxime as white crystals, mp 98.5-101 °C.

30

To a solution of 3.0 g (7.4 mmol) of the above oxime and 0.5 g (7.9 mmol) of sodium cyanoborohydride in 30 ml of methanol was added 3 mg of methyl orange. To the resulting solution was added dropwise a solution of conc. HCl and methanol (1:1) at a rate to maintain a reddish

35

color (pH~ 3.4). After the red color remained (1 h) the reaction mixture was partitioned between ether and 10% NaOH. The organic was washed with brine, dried (MgSO₄), and filtered through silica gel, and the filtrate was concentrated in vacuo. The residue was purified by HPLC (35% EtOAc in hexane) to give two fractions. The first fraction amounted to 0.8 g (27% yield) of crystals which was the desired product, mp 141.5-143.5 °C. The second fraction amounted to 1.5 g (50% yield) of a colorless oil identified as the other diastereomer.

Example 43

Preparation of Ethyl 4-Hydroxy-5-phenoxy-6-(trifluoromethyl)-3-pyridine-carboxylate (Compound 109)

Ethyl 2-(1-amino-2,2,2-trifluoroethylidien)-3-oxo-4-phenoxy-butanoate (example B1 of U.S. patent 4,936,905) was reacted according to the procedure in step 1 of Example 28 to give the product.

Example 44

Preparation of Methyl 2-(difluoromethyl)-4-(2-methylpropyl)-5-(2-oxazolyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 110)

This compound was prepared according to the procedure in example 4 of U.S. patent 4,988,384 except ethanolamine was used instead of glycine methyl ester hydrochloride.

Example 45

Preparation of Methyl 5-(Chloroethylsulfinyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 111)

Oxidation of compound 44 with one equivalent of MCPBA according to the procedure in example 21 of U.S. patent

212

4,789,395 gave the product.

Example 46

Preparation of Methyl 4-(Cyclopropylmethyl)-2-

5 (difluoromethyl)-5-[imino(methylthio)methyl]-
6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 112)

Step 1: Methyl 5-(aminothioxomethyl)-4-(Cyclopropyl-
methyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-
10 pyridinecarboxylate.

Methyl 5-chlorocarbonyl-4-(cyclopropylmethyl)-2-
(difluoromethyl)-6-(trifluoromethyl)-3-pyridine-
carboxylate (example B3 of U.S. patent 5,156,670) was
15 converted to methyl 4-(cyclopropylmethyl)-5-cyano-2-
(difluoromethyl)-6-(trifluoromethyl)-3-pyridine-
carboxylate by the procedure similar to example 88 and 92
of U.S. patent 4,692,184. A solution of 20 g (60 mmol) of
this cyano compound and 0.62 g (6 mmol) of diethylamine
20 in 60 ml of DMF was heated to 50 °C. Hydrogen sulfide gas
was introduced into this solution. When absorption of
hydrogen sulfide was complete the reaction mixture was
stirred at 50 °C for 1 h and poured into water and
extracted with ether. The ether extract was washed with
25 brine, dried (MgSO₄), and concentrated in vacuo. The
residue was kugelrohr distilled to give 17.7 g (80%
yield) of yellow oil.

Step 2: Methyl 4-(Cyclopropylmethyl)-2-(difluoromethyl)-
30 5-[imino(methylthio)methyl]- 6-(trifluoromethyl)-3-
pyridinecarboxylate (Compound 112)

A solution of 3.7 g (10 mmol) of product of step 1 in 20
ml of methylene chloride was treated with 1.24 ml (11
35 mmol) of methyl trifluoromethylsulfonate. The reaction
mixture as stirred under nitrogen at room temperature

213

overnight and diluted with 80 ml of methylene chloride and washed with a saturated sodium bicarbonate solution. The methylene chloride solution was dried (MgSO₄), and concentrated in vacuo. The residue was purified by
5 chromatography (EtOAc: hexane = 1:5) to give 2.30 g (60%) of a yellow oil, n²⁵D 1.5059.

Compound 90 in Table 1 was similarly prepared except using methyl 5-(chlorocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate
10 as the reagent.

Example 47

Preparation of Ethyl 5-Ethoxy-4-Hydroxy-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 114)

15 Ethyl 3-amino-2-(2-ethoxy-1-oxo-ethyl)-4,4,4-trifluoro-2-butenate (example A2 of U.S. patent 4,936,905) was reacted according to the procedure in step 1 of example 28 to give the product.

20

Example 48

Methyl 5-{[2-Chloro-4-(trifluoromethyl)-5-thiazolyl] carbonylamino}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 117)

25

Methyl 5-amino-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example A1 of U.S. patent 5,114,465) was reacted with 2-chloro-4-(trifluoromethyl)-5-thiazolecarbonyl chloride according
30 to the procedure in example 1 of U.S. patent 5,114,465 afforded the product.

Example 49

Preparation of Methyl 5-(aminothioxomethyl)-4-(cyclobutyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 119)

5

This compound was prepared from methyl 5-(chloro-carbonyl)-4-(cyclobutyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate according to the procedure in step 1 of Example 46.

10

Compound 103 in Table 2 was made similarly except using methyl 5-chlorocarbonyl-4-(2-methylpropyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (step 7 of U.S. Patent 4,988,384) as the starting material.

15

Example 50

Preparation of 4-(4-Isopropylphenylthio)-5-methyl-6-(trifluoromethyl)-3-pyridinecarboxylic Acid (Compound 126)

20

Methyl 4-(4-isopropylphenylthio)-5-methyl-6-(trifluoromethyl)-3-pyridinecarboxylate (compound 11) was hydrolyzed with sodium hydroxide to give the product.

25

Example 51

Methyl 5-(aminoethylthiocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 134)

30

Reaction of methyl 5-(chlorocarbonyl)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (step 7 of U.S. patent 4,988,384) with 2-mercaptoethylamine similar to the procedure in example 140 of U.S. patent 4,692,184 gave the product.

35

Example 52

Preparation of Methyl 5-(1-Bromo-2-methoxyethenyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 35)

5 To a solution of 18.0 g (49.3 mmol) of methyl 4-(cyclopropylmethyl)-2-(difluoromethyl)-5-(2-methoxyethenyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 127 of U.S. patent 6,169,432) in 250 ml of ether was added 7.9 g
10 (49.4 mmol) of bromine. The reaction mixture was stirred at room temperature for 2 h and to the mixture was added 6.8 g of freshly ground potassium carbonate and 100 ml of methanol. The reaction mixture was stirred for another 45 min and was washed with water and brine. The organic
15 layer was dried (MgSO₄), filtered through celite, and concentrated in vacuo. The residue was kugelrohr distilled and the distillate was purified by chromatography (7% EtOAc in hexane) to give 18.7 g (80% yield) of 1:1 mixture of methyl 5-(1-bromo-2,2-dimethoxy-
20 ethyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate and product. HPLC purification (10% EtOAc in hexane) gave 4.1 g of the desired product as a colorless oil which crystallized and was recrystallized from hexane to give crystals, mp
25 79-79.5 °C.

Example 52

Preparation of Methyl 2-(Difluoromethyl)-5-[(dimethylaminothionothio)methyl]-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 43)

30

To a solution of 0.91 g (20 mmol) of dimethylamine in 6 ml of water and 0.92 g of 50% NaOH at 0 °C was added 0.95 g (12.5 mmol) of carbon disulfide. The reaction mixture
35 was stirred for 1 h and to the reaction mixture was added a solution of 3.6 g (10 mmol) of 5-chloromethyl-2-

216

(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate (example 3 of U.S. patent 5,169,432) in 10 ml of acetone. The reaction mixture was quenched with water, extracted with methylene chloride, dried (MgSO₄), filtered through celite, and concentrated in vacuo. The residual brown solid was crystallized from ethyl acetate- hexane to give 3.21 g (72% yield) of product, mp 91-92 °C.

10

Example 53

Preparation of Methyl 2-(Difluoromethyl)-5-[(dimethyl-aminothionoethio)methyl]-6-(trifluoromethyl)-3-pyridinecarboxylate (Compound 79)

15

This compound was made by the procedure similar to example 52 except gaseous carbonyl sulfide was used to replace carbon disulfide. The product was isolated as white power, mp 80-81 °C.

20

Biological Activity ExamplesExample 54CETP Activity In Vitro

The ability of compounds to inhibit CETP were assessed using an *in vitro* assay that measured the rate of transfer of radiolabeled cholesteryl ester ([³H]CE) from HDL donor particles to LDL acceptor particles. Details of the assay are provided by Glenn et al. ("Quantification of Cholesteryl Ester Transfer Protein (CETP): A) CETP Activity and B) Immunochemical Assay of CETP Protein," *Meth. Enzymol.*, Glenn and Melton (*Meth. Enzymol.*, 263, 339-351 (1996), which is incorporated herein by reference). CETP was obtained from the serum-free conditioned medium of CHO cells transfected with a cDNA for CETP (Wang, S. et al. *J. Biol Chem.* 267, 17487-17490 (1992), which is incorporated herein by

reference).

To measure CETP activity, [³H]CE-labeled HDL, LDL, CETP and assay buffer (50 mM tris(hydroxymethyl)amino-methane, pH 7.4; 150 mM sodium chloride; 2 mM
5 ethylenediamine-tetraacetic acid; 1% bovine serum albumin) were incubated in a volume of 200 μ l, for 2 hours at 37°C in 96 well plates. LDL was differentially precipitated by the addition of 50 μ l of 1% (w/v) dextran sulfate/0.5 M magnesium chloride, mixed by vortex, and
10 incubated at room temperature for 10 minutes. The solution (200 μ l) was transferred to a filter plate (Millipore). After filtration, the radioactivity present in the precipitated LDL was measured by liquid scintillation counting. Correction for non-specific
15 transfer or precipitation was made by including samples that did not contain CETP. The rate of [³H]CE transfer using this assay was linear with respect to time and CETP concentration, up to 25-30% of [³H]CE transferred.

The potency of test compounds was determined by
20 performing the above described assay in the presence of varying concentrations of the test compounds and determining the concentration required for 50% inhibition of transfer of [³H]CE from HDL to LDL. This value was defined as the IC₅₀. The IC₅₀ values determined by this
25 method for the substituted pyridine compounds of the invention are specified in Tables 1-8.

Example 55

30 Whole Serum CETP Activity Assay (Tritiated Cholesterol Ester)

Blood was obtained from healthy volunteers recruited from the personnel of Monsanto Company, Saint Louis, MO. Blood was either collected in tubes containing EDTA (EDTA plasma pool) or in tubes without EDTA (spun to form the
35 serum pool). The EDTA human plasma pool or human serum pool, previously stored at -20°C, was thawed at room

temperature, and centrifuged for 5 minutes to remove any particulate matter. Tritiated HDL, radiolabeled in the cholesteryl ester moiety ($[^3\text{H}]\text{CE-HDL}$) as described by Morton and Zilversmit (J. Biol. Chem., 256, 11992-95 (1981) which is incorporated by reference herein), was added to the plasma or serum to a final concentration of (25 $\mu\text{g/ml}$ cholesterol).

Inhibitor compounds were added to the plasma or serum as follows: Equal volumes of the plasma or serum containing the $[^3\text{H}]\text{CE-HDL}$ (396 μl) were pipetted into micro tubes (Titertube[®], Bio-Rad Laboratories, Hercules, CA). Compounds, usually dissolved as 20-50 mM stock solutions in DMSO, were serially diluted in DMSO (or an alternative solvent in some cases, such as dimethylformamide or ethanol). Four μl of each of the serial dilutions of inhibitor compounds or DMSO alone were then added to each of the plasma or serum tubes. The tubes were immediately mixed. Triplicate aliquots (100 μl) from each plasma or serum tube were then transferred to wells of 96-well round-bottomed polystyrene microtiter plates (Corning, Corning, NY). Plates were sealed with plastic film and incubated at 37 °C for 4 hours.

Test wells contained plasma or serum with dilutions of inhibitor compounds. Control wells contained plasma or serum with DMSO alone. Blank wells contained plasma or serum with DMSO alone that were left in the micro tubes at 4°C for the 4 hour incubation and were added to the microtiter wells at the end of the incubation period. VLDL and LDL were precipitated by the addition of 10 μl of precipitating reagent (1% (w/v) Dextran Sulfate (Dextralip50)/0.5M magnesium chloride, pH 7.4) to all wells. The wells were mixed on a plate mixer and then incubated at ambient temperature for 10 min. The plates were then centrifuged at 1000 x g for 30 mins at 10°C. The supernatants (50 μl) from each well were then

transferred to Picoplate™ 96 plate wells (Packard, Meriden, CT) containing 250:1 Microscint™-40 (Packard, Meriden, CT). The plates were heat-sealed (TopSeal™-P, Packard, Meriden, CT) according to the manufacturers
5 directions and mixed for 30 min.

Radioactivity was measured on a microplate scintillation counter (TopCount, Packard, Meriden, CT). IC₅₀'s were determined as the concentration of inhibitor compound inhibiting transfer of [³H]CE from the
10 supernatant [³H]CE-HDL to the precipitated VLDL and LDL by 50% compared to the transfer obtained in the control wells. The maximum percent transfer (in the control wells) was determined using the following equation:

$$15 \quad \% \text{ Transfer} = \frac{[\text{dpm}_{\text{blank}} - \text{dpm}_{\text{control}}] \times 100}{\text{dpm}_{\text{blank}}}$$

20 The percent of control transfer determined in the wells containing inhibitor compounds was determined as follows:

$$25 \quad \% \text{ Control} = \frac{[\text{dpm}_{\text{blank}} - \text{dpm}_{\text{test}}] \times 100}{\text{dpm}_{\text{blank}} - \text{dpm}_{\text{control}}}$$

IC₅₀ values were then calculated from plots of %
30 control versus concentration of inhibitor compound. The IC₅₀ values of the substituted pyridine compounds determined by this method are as follows: Compound 7, 17 micromolar; Compound 180, 9 micromolar; Compound 181, 16 micromolar; Compound 214, 70 micromolar; and Compound
35 215, 110 micromolar.

Example 56**Inhibition of CETP Activity In Vivo**

Inhibition of CETP by a test compound can be determined by administering the compound to an animal by intravenous injection, determining the rate of transfer of tritium-labeled cholesteryl ester (^3H]CE) from HDL to VLDL and LDL particles, and comparing the rate of transfer with the rate of transfer observed in control animals.

- Male golden Syrian hamsters were maintained on a diet of chow containing 0.24% cholesterol for at least two weeks prior to the study. Immediately before the experiment, animals were anesthetized with pentobarbital. Anesthesia was maintained throughout the experiment.
- Indwelling catheters were inserted into the jugular vein and carotid artery. Test compound, Dimethyl 5,5'-dithiobis[2-difluoromethyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate] (Compound 181), was dissolved as a 80 mM stock solution in vehicle (2% ethanol: 98% PEG 400, Sigma Chemical Company, St. Louis, Missouri, USA). At the start of the experiment all animals received 0.2 ml of a solution containing [^3H]-CE-HDL into the jugular vein. [^3H]-CE-HDL is a preparation of human HDL containing tritium-labeled cholesteryl ester, and was prepared according to the method of Glenn et al. ("Quantification of Cholesteryl Ester Transfer Protein (CETP): A) CETP Activity and B) Immunochemical Assay of CETP Protein," *Meth. Enzymol.*, Glenn and Melton (*Meth. Enzymol.*, 263, 339-351 (1996) which is incorporated herein by reference).

- After 2 minutes, the animals received 0.1 ml of the test solution injected into the jugular vein. Control animals received 0.1 ml of the vehicle solution without test compound. After 5 minutes, the first blood samples (0.5 ml) were taken from the carotid artery and collected in standard microtainer tubes containing ethylenediamine

tetraacetic acid. Saline (0.5 ml) was injected to flush the catheter and replace blood volume. Subsequent blood samples were taken at two hours and four hours by the same method. Blood samples were mixed well and kept on ice until the completion of the experiment.

Plasma was obtained by centrifugation of the blood samples at 4° C. The plasma (50 μ l) was then treated with 5 μ l of precipitating reagent (dextran sulfate, 10 g/l; 0.5M magnesium chloride to remove VLDL/LDL. After centrifugation, the resulting supernatant (25 μ l) containing the HDL was analyzed for radioactivity using a liquid scintillation counter. The percentage [3 H] CE transferred from HDL to LDL and VLDL (% transfer) was calculated based on the total radioactivity in equivalent serum samples before precipitation. Typically, the amount of transfer from HDL to LDL and VLDL in control animals was 30 to 35% after four hours. The polyethylene glycol vehicle was determined to have no effect on CETP activity in this model.

Table 14 shows the results of an experiment utilizing five animals that received Dimethyl 5,5'-dithiobis[2-difluoromethyl]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate] (Compound 181), and five animals that received vehicle. At two hours, mean values of 13% [3 H]-Ce transfer from HDL to LDL and VLDL were obtained for the control animals, but only 4.7% transfer for the animals receiving Compound 181. This represents a 64% inhibition of CETP activity. Student t-tests were performed to determine if the means for control and animals treated with Compound 181 were statistically different. Values of $p < 0.01$ for both sets of data indicate that the differences are highly significant.

222

TABLE 14

		% Transfer		% Inhibition	
		<u>Control</u>	<u>Compound 181</u>	<u>Compound 181</u>	<u>t-Test</u>
5	Two Hours	13	4.7	63.6	0.008
	Four hours	21.6	10.6	50.8	0.001

Similarly, in separate experiments a mean of 21.6% [³H]-CE transfer was obtained for the control animals at
 10 four hours, but only 10.6% was transferred in animals treated with methyl 2-(difluoromethyl)-5-mercapto-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-carboxylate (Compound 7), representing a 50% inhibition of CETP activity.

15

Example 57**Chronic Inhibition of CETP Activity In Vivo**

Chronic inhibition of CETP can be achieved by administration of Dimethyl 5,5'-dithiobis[2-
 20 difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate] (Compound 181) to hamsters using Alzet pump delivery of Compound 181 into the jugular veins of hamsters. Inhibition of CETP should lead to an increase in HDL cholesterol with a concomitant decrease
 25 in LDL cholesterol. This can be determined by filtering serum obtained at different time intervals after initiation of inhibitor infusion and quantitating the amount of cholesterol in the LDL and HDL peaks, respectively. In addition the activity of CETP in the
 30 serum can be assessed in an ex vivo CETP activity assay.

Male golden Syrian hamsters were maintained on a diet of normal rodent chow enriched with 0.24% cholesterol for at least 2 weeks prior to study. On Day 1, the hamsters were anesthetized with pentobarbital. An
 35 indwelling catheter was inserted into the jugular vein and exteriorized onto the back of the neck. The hamsters

received 100 μ of Compound 181 (38.5 mg/kg) in a 2% ethanol:98% PEG400 vehicle, or the 2% ethanol:98% PEG400 vehicle alone. An Alzet pump was then attached to the jugular catheter which delivered a steady infusion of 24 μ l/day for a dose of 1.3 mg/day (9.2 mg/kg/day). The hamsters received the vehicle (2% ETOH:98% PEG400) or Compound 181 for 8 days. The hamsters were maintained for 12 days. Blood samples were taken on day 1 (pre-bleed) at the time of surgery, and on days 5, 7, 8 and 12. Fast Protein Liquid Chromatography (FPLC) on tandem Superose 6 columns of pooled hamster serum was performed to obtain cholesterol profiles for the two experimental groups.

Table 15 shows the results of an experiment utilizing 5 hamsters in each group, vehicle and Compound 181. Serum cholesterol profiles were determined on pooled sera from each group. Total serum cholesterol and CETP activity were determined on individual serum samples. In hamsters administered Compound 181 chronically, there was a 30% reduction and 26% increase in LDL cholesterol and HDL cholesterol concentrations, respectively, compared to the vehicle group at Day 5. The decrease in LDL and increase in HDL persisted until Day 8 when the Alzet pump was exhausted. At Day 12, LDL cholesterol concentrations began to rise and HDL cholesterol concentrations started to decrease toward the concentrations in the vehicle group (90% and 114% of vehicle group, respectively). It should be noted that an average 10% reduction in CETP activity was determined by ex vivo assay on Days 5 and 8 with a return to vehicle control level by day 12. Therefore, it would appear that for every percent reduction in CETP activity determined by the ex vivo assay, there was a 2-3% decrease in LDL cholesterol or increase in HDL cholesterol concentrations.

TABLE 15

Cholesterol Concentrations In Compound 181

% Cholesterol Concentration In Vehicle Group		
DAY	LDL	HDL
Day 1	111%	105%
Day 5	70%	126%
Day 8	75%	115%
Day 12	90%	114%

The foregoing biological data demonstrate that administration of the substituted pyridine inhibitors of the present invention produces inhibition of CETP-mediated lipid transfer in vivo.

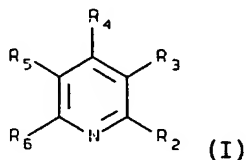
5 All mentioned references are incorporated by reference as if here written.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

10 As various changes could be made in the above compositions and processes without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A method for inhibiting the activity of cholesteryl ester transfer protein *in vivo* by administering to a subject a therapeutically effective amount of a compound of Formula I:



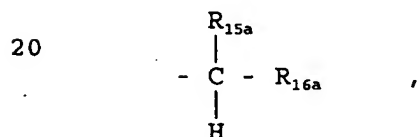
wherein:

R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxy carbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl

-CHO,

-CO₂R₇, wherein R₇ is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and



wherein R_{15a} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio,

heterocyclylthio, alkoxy, alkenoxy, alkynoxy,
aryloxy, heteroaryloxy and heterocyclyoxy, and

30 R_{16a} is selected from the group consisting of
alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl,
haloalkynyl, aryl, heteroaryl, and heterocyclyl,
arylalkoxy, trialkylsilyloxy;

R_4 is selected from the group consisting of hydrogen,
hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl,
35 cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl,
heteroaryl, heterocyclyl, cycloalkylalkyl,
cycloalkenylalkyl, aralkyl, heteroarylalkyl,
heterocyclylalkyl, cycloalkylalkenyl,
cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
40 heterocyclylalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy,
heteroaryloxy, heterocyclyoxy, alkanoyloxy, alkenoyloxy,
alkynoyloxy, aryloyloxy, heteroaroxyloxy,
heterocyclyoxyloxy, alkoxycarbonyl, alkenoxycarbonyl,
alkynoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl,
45 heterocyclyoxy carbonyl, thio, alkylthio, alkenylthio,
alkynylthio, arylthio, heteroarylthio, heterocyclylthio,
cycloalkylthio, cycloalkenylthio, alkylthioalkyl,
alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
heteroarylthioalkyl, heterocyclylthioalkyl,
50 alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,
arylthioalkenyl, heteroarylthioalkenyl,
heterocyclylthioalkenyl, alkylamino, alkenylamino,
alkynylamino, arylamino, heteroarylamino,
heterocyclylamino, aryldialkylamino, diarylamino,
55 diheteroarylamino, alkylarylamino, alkylheteroarylamino,
arylheteroarylamino, trialkylsilyl, trialkenylsilyl,
triarylsilyl,

$-OC(O)N(R_{8a}R_{8b})$, wherein R_{8a} and R_{8b} are
independently selected from the group consisting of
60 alkyl, alkenyl, alkynyl, aryl, heteroaryl and
heterocyclyl,

-SO₂R₉, wherein R₉ is selected from the group consisting of hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl,

65 -OP(O)(OR_{10a})(OR_{10b}), wherein R_{10a} and R_{10b} are independently selected from the group consisting of hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl, and

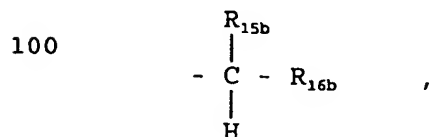
70 -OP(S)(OR_{11a})(OR_{11b}), wherein R_{11a} and R_{11b} are independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

R₅ is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, 75 cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocycliloxy, alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl, alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl, 80 heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl, cycloalkylalkyl, cycloalkenylalkyl, aralkyl, heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl, cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl, heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl, 85 alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl, heteroarylthioalkyl, heterocyclylthioalkyl, alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl, arylthioalkenyl, heteroarylthioalkenyl, heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl, 90 alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, heterocycliloxyalkyl, alkoxyalkenyl, alkenoxyalkenyl, alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl, heterocycliloxyalkenyl, cyano, hydroxymethyl,

95 -CO₂R₁₄,

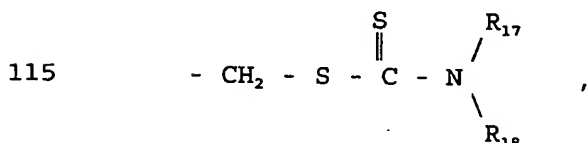
228

wherein R_{14} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

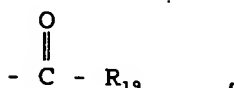


105 wherein R_{15b} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocycliloxy, aroyloxy, and alkylsulfonyloxy, and

110 R_{16b} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkoxy, and trialkylsilyloxy;



120 wherein R_{17} and R_{18} are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



125 wherein R_{19} is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-SR_{20}$, $-OR_{21}$, and $-R_{22}CO_2R_{23}$, wherein

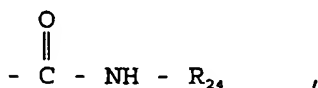
130 R_{20} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl,

aminoalkynyl, aminoaryl, aminoheteroaryl,
aminoheterocyclyl, alkylheteroarylmino,
arylheteroarylmino,

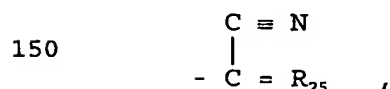
135 R_{21} is selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl,

R_{22} is selected from the group consisting of
alkylene or arylene, and

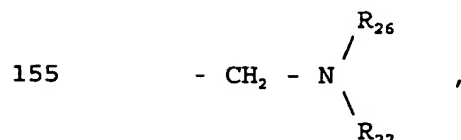
140 R_{23} is selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl;



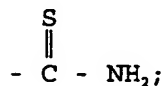
145 wherein R_{24} is selected from the group
consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl,
aralkenyl, and aralkynyl;



150 wherein R_{25} is heterocyclylidenyl;

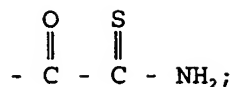


155 wherein R_{26} and R_{27} are independently selected
from the group consisting of hydrogen, alkyl,
160 cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl;

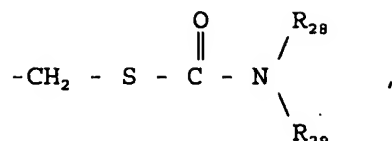


230

165



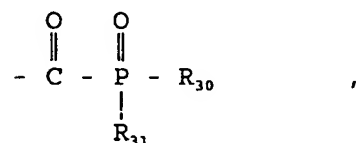
170



175

wherein R_{28} and R_{29} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

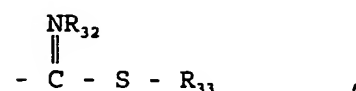
180



185

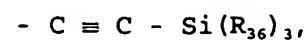
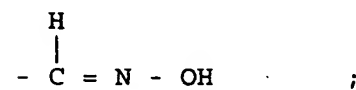
wherein R_{30} and R_{31} are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocyclyloxy; and

190



wherein R_{32} and R_{33} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

195

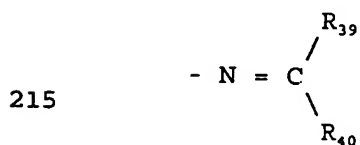


231

200 wherein R_{36} is selected from the group
consisting of alkyl, alkenyl, aryl, heteroaryl and
heterocyclyl;



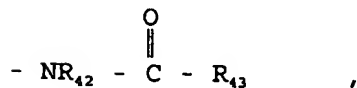
210 wherein R_{37} and R_{38} are independently selected
from the group consisting of hydrogen, alkyl,
cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl;



220 wherein R_{39} is selected from the group
consisting of hydrogen, alkoxy, alkenoxy, alkynoxy,
aryloxy, heteroaryloxy, heterocycliloxy, alkylthio,
alkenylthio, alkynylthio, arylthio, heteroarylthio
and heterocyclylthio, and

225 R_{40} is selected from the group consisting of
haloalkyl, haloalkenyl, haloalkynyl, haloaryl,
haloheteroaryl, haloheterocyclyl, cycloalkyl,
cycloalkenyl, heterocyclylalkoxy,
heterocyclylalkenoxy, heterocyclylalkynoxy,
alkylthio, alkenylthio, alkynylthio, arylthio,
heteroarylthio and heterocyclylthio;

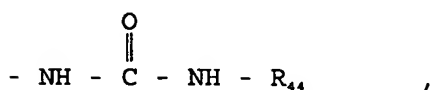
230 $- N = R_{41}$,
wherein R_{41} is heterocyclylidenyl;



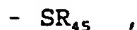
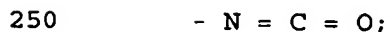
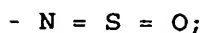
232

235 wherein R_{42} is selected from the group
consisting of hydrogen, alkyl, alkenyl, alkynyl,
aryl, heteroaryl, and heterocyclyl, and

240 R_{43} is selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl,
heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl,
haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl,
and haloheterocyclyl;



245 wherein R_{44} is selected from the group
consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
alkynyl, aryl, heteroaryl and heterocyclyl;



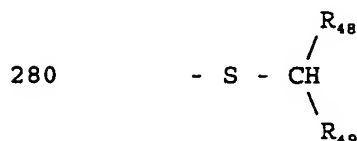
255 wherein R_{45} is selected from the group
consisting of hydrogen, alkyl, alkenyl, alkynyl,
aryl, heteroaryl, heterocyclyl, haloalkyl,
haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl,
haloheterocyclyl, heterocyclyl, cycloalkylalkyl,
cycloalkenylalkyl, aralkyl, heteroarylalkyl,
heterocyclylalkyl, cycloalkylalkenyl,
260 cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
heterocyclylalkenyl, alkylthioalkyl,
alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,

233

heteroarylthioalkyl, heterocyclylthioalkyl,
 alkylthioalkenyl, alkenylthioalkenyl,
 265 alkynylthioalkenyl, arylthioalkenyl,
 heteroarylthioalkenyl, heterocyclylthioalkenyl,
 aminocarbonylalkyl, aminocarbonylalkenyl,
 aminocarbonylalkynyl, aminocarbonylaryl,
 aminocarbonylheteroaryl, and
 270 aminocarbonylheterocyclyl,
 -SR₄₆, and -CH₂R₄₇,

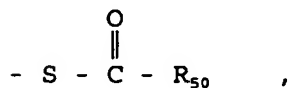
wherein R₄₆ is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl, and

275 R₄₇ is selected from the group consisting of
 hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl
 and heterocyclyl; and



wherein R₄₈ is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 285 alkynyl, aryl, heteroaryl and heterocyclyl, and

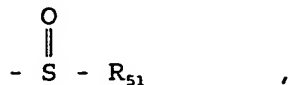
R₄₉ is selected from the group consisting of
 alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy,
 heterocyclyloxy, haloalkyl, haloalkenyl,
 haloalkynyl, haloaryl, haloheteroaryl and
 290 haloheterocyclyl;



wherein R₅₀ is selected from the group
 295 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy,
 alkenoxy, alkynoxy, aryloxy, heteroaryloxy and

heterocyclyloxy;

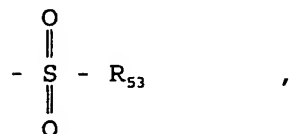
300



305

wherein R_{51} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and

310



wherein R_{53} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

315

or a pharmaceutically acceptable salt or tautomer thereof,

320

provided that when R_5 is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, the heterocyclyl radical of the corresponding heterocyclylalkyl or heterocyclylalkenyl is other than a δ -lactone; and

provided that when R_4 is aryl, heteroaryl or heterocyclyl, and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.

2. The method of claim 1 wherein:

R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated

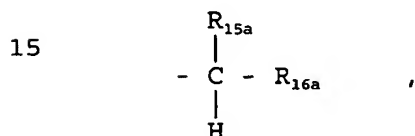
235

alkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl,
 5 aryl, heteroaryl, alkoxy, alkoxyalkyl, and
 alkoxycarbonyl; provided that at least one of R_2 and R_6 is
 fluorinated alkyl, chlorofluorinated alkyl or
 alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy,
 10 amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,

$-\text{CO}_2R_7$,

wherein R_7 is selected from the group consisting
 of hydrogen, alkyl and cyanoalkyl; and



wherein R_{15a} is selected from the group
 20 consisting of hydroxy, halogen, alkylthio and
 alkoxy, and

R_{16a} is selected from the group consisting of
 alkyl, aryl and heteroaryl;

R_4 is selected from the group consisting of hydrogen,
 25 hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl,
 aryl, heteroaryl, cycloalkylalkyl, heteroarylalkyl,
 aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl,
 arylcarbonyloxy, thio, alkylthio, arylthio,
 cycloalkylthio, heterocyclylthio, alkylthioalkyl,
 30 alkylamino, trialkylsilyl,

$-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl,

$-\text{SO}_2\text{R}_9$, wherein R_9 is aryl,

$-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl, and

$-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl;

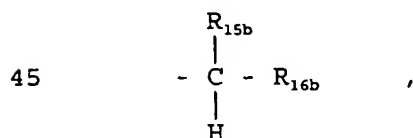
35 R_5 is selected from the group consisting of hydrogen,

236

hydroxy, halogen, alkyl, haloalkyl, alkynyl,
 heterocyclyl, heteroaryl, alkoxy, aryloxy,
 arylcarbonyloxyalkyl, heterocyclylalkyl, alkylthioalkyl,
 arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, cyano,
 40 hydroxymethyl,

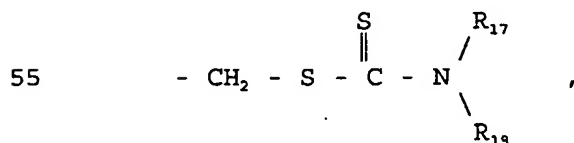


wherein R_{14} is alkyl;

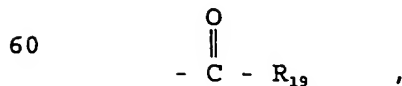


wherein R_{15b} is selected from the group
 consisting of hydroxy, hydrogen, halogen, alkylthio
 50 and alkoxy, and

R_{16b} is selected from the group consisting of
 alkyl, aryl and heteroaryl;



wherein R_{17} and R_{18} are independently alkyl;



wherein R_{19} is selected from the group
 consisting of aryl, heteroaryl, $-\text{SR}_{20}$, $-\text{OR}_{21}$, and
 $-\text{R}_{22}\text{CO}_2\text{R}_{23}$,

65 wherein R_{20} is selected from the group
 consisting of alkyl, aryl and aminoalkyl,

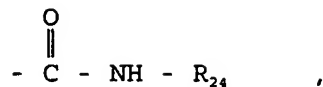
R_{21} is aryl,

R_{22} is alkylene, and

237

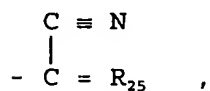
R_{23} is alkyl;

70



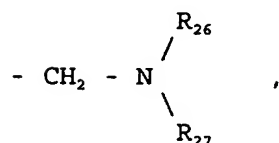
wherein R_{24} is selected from the group consisting of hydrogen, unsubstituted alkyl, and aralkyl;

75



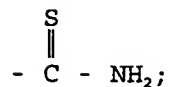
wherein R_{25} is heterocyclylidenyl;

80

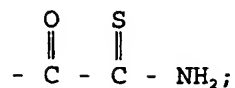


85

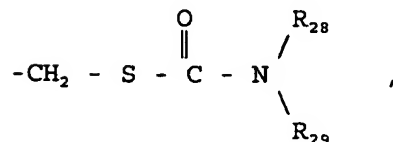
wherein R_{26} and R_{27} are independently alkyl;



90



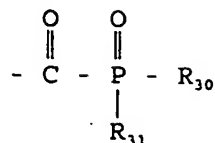
95



wherein R_{28} and R_{29} are independently alkyl;

238

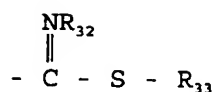
100



105

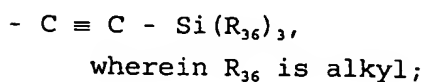
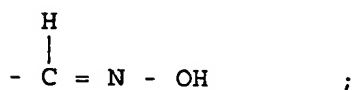
wherein R_{30} and R_{31} are independently alkoxy;

110

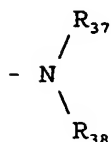


wherein R_{32} is selected from the group consisting of hydrogen and alkyl, and R_{33} is alkyl;

115

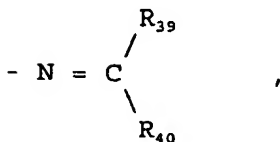


120



wherein R_{37} and R_{38} are independently alkyl;

125

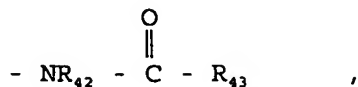


130

wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and R_{40} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

239

135 - N = R₄₁, wherein R₄₁ is heterocyclylidenyl;



140 wherein R₄₂ is selected from the group consisting of hydrogen and alkyl, and
 R₄₃ is selected from the group consisting of cycloalkyl, chlorinated alkyl and substituted heteroaryl;

145 - NH - $\overset{\text{O}}{\parallel} \text{C}$ - NH - R₄₄ ,
 wherein R₄₄ is heteroaryl;

- N = S = O;

- N = C = S;

150 - N = C = O;

- N₃;

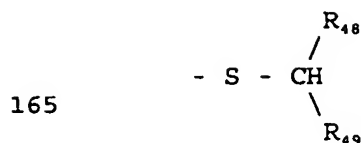
- SR₄₅ ,

155 wherein R₄₅ is selected from the group consisting of hydrogen, alkyl, haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, alkylthioalkyl, aminocarbonylalkyl, -SR₄₆, and -CH₂R₄₇,

wherein R₄₆ is selected from the group consisting of aryl and heteroaryl, and

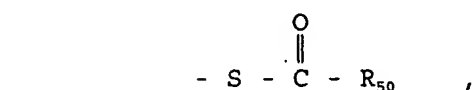
160 R₄₇ is selected from the group consisting of aryl and heteroaryl; and

240

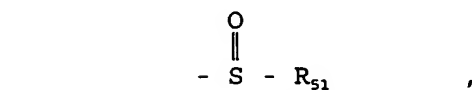


wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

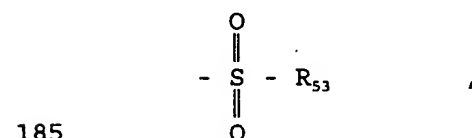
170 R_{49} is selected from the group consisting of alkoxy and haloalkyl;



wherein R_{50} is selected from the group consisting of alkyl, alkoxy, aryl and heteroaryl;



wherein R_{51} is selected from the group consisting of haloalkyl and alkyl; and



wherein R_{53} is aryl;

or a pharmaceutically acceptable salt or tautomer thereof,

190 provided that when R_5 is heterocyclalkyl or heterocyclalkenyl, then the heterocycl radical is other than a δ -lactone and the alkyl or alkenyl radical is other than $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}=\text{CH}-$.

3. The method of claim 2 wherein:

- when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is $-\overset{\text{O}}{\parallel}\text{C}-\text{R}_{19}$,
 5 R_6 is trifluoromethyl, and R_{19} is the heteroaryl 1-pyrazolyl, then R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkoxy, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy,
 10 alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, trialkylsilyl,
 $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl,
 $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl,
 15 $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl, and
 $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl; and

- when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is the heterocyclyl 2-(4,5-dihydro-oxazolyl), and R_6 is trifluoromethyl, then R_4 is selected from the group
 20 consisting of hydrogen, hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, heteroarylalkyl, aralkenyl, alkoxy, aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio, arylthio, cycloalkylthio, heterocyclylthio,
 25 alkylthioalkyl, alkylamino, trialkylsilyl,
 $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl,
 $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl,
 $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl, and
 $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl; and

- 30 when R_2 and R_6 are independently fluorinated methyl, R_3 is $-\text{CO}_2\text{R}_7$, R_5 is cyano, and R_7 is selected from the group consisting of hydrogen and alkyl, then R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, cycloalkyl, haloalkyl, heteroaryl,

- 35 cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy,
 aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio,
 alkylthio, arylthio, cycloalkylthio, heterocyclylthio,
 alkylthioalkyl, alkylamino, trialkylsilyl,
 $-OC(O)N(R_8)_2$, wherein R_8 is aryl,
 40 $-SO_2R_9$, wherein R_9 is aryl,
 $-OP(O)(OR_{10})_2$, wherein R_{10} is alkyl, and
 $-OP(S)(OR_{11})_2$, wherein R_{11} is alkyl; and

- 45 when R_2 is methyl, R_3 is $-CO_2C_2H_5$, R_5 is $-C(=O)NH-R_{24}$, R_6
 is methyl, and R_{24} is aralkyl, then R_4 is selected from
 the group consisting of hydroxy, halogen, alkyl,
 cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl,
 cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy,
 50 aralkoxy, alkoxycarbonyl, arylcarbonyloxy, thio,
 alkylthio, arylthio, cycloalkylthio, heterocyclylthio,
 alkylthioalkyl, alkylamino, trialkylsilyl,
 $-OC(O)N(R_8)_2$, wherein R_8 is aryl,
 $-SO_2R_9$, wherein R_9 is aryl,
 55 $-OP(O)(OR_{10})_2$, wherein R_{10} is alkyl, and
 $-OP(S)(OR_{11})_2$, wherein R_{11} is alkyl, and

- when R_2 is methyl, R_3 and R_5 are $-CO_2C_2H_5$, and R_4 is
 alkoxy, then R_6 is selected from the group consisting of
 hydrogen, hydroxy, alkyl comprising at least two carbon
 60 atoms, fluorinated alkyl, chlorofluorinated alkyl,
 alkoxy, alkoxyalkyl, and alkoxycarbonyl,

- when R_2 is difluoromethyl, R_3 is $-CO_2R_7$, R_4 is
 alkenyl, R_5 is CO_2CH_3 , and R_6 is trifluoromethyl, then R_7
 is selected from the group consisting of alkyl and
 65 cyanoalkyl,

when R_2 is methyl, R_4 is hydrogen, R_5 is $CO_2C_2H_5$, and

R_6 is methyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, 70 alkyl comprising at least three carbon atoms, and cyanoalkyl,

when R_2 is difluoromethyl, R_4 is hydrogen, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2R_7$, 75 wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms, and cyanoalkyl,

when R_2 is difluoromethyl, R_4 is alkylthioalkyl, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, then R_3 is selected 80 from the group consisting of hydroxy, amido and $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of alkyl and cyanoalkyl,

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_4 is alkyl, R_5 is $-\text{CO}_2\text{CH}_3$, then R_6 is selected from the group 85 consisting of hydrogen, hydroxy, alkyl comprising at least two carbon atoms, fluorinated alkyl, chlorofluorinated alkyl, alkoxy, alkoxyalkyl, and alkoxycarbonyl,

when R_2 is difluoromethyl, R_4 is alkyl, R_5 is $-\text{CO}_2R_{14}$, 90 R_6 is trifluoromethyl, and R_{14} is alkyl, then R_3 is selected from the group consisting of hydroxy and $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen, alkyl and cyanoalkyl,

when R_2 is selected from the group consisting of 95 hydroxy and trifluoromethyl, R_4 and R_5 are hydrogen, and R_6 is selected from the group consisting of methyl and trifluoromethyl, then R_3 is selected from the group

consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is
 100 selected from the group consisting of alkyl and
 cyanoalkyl,

when R_2 is selected from the group consisting of
 methyl, difluoromethyl and trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$,
 R_5 is hydrogen, and R_6 is selected from the group
 consisting of methyl and trifluoromethyl, then R_4 is
 105 selected from the group consisting of hydrogen, hydroxy,
 halogen, cycloalkyl, alkenyl, aryl, heteroaryl,
 cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy,
 aralkoxy, alkoxycarbonyl, thio, alkylthio, arylthio,
 cycloalkylthio, heterocyclylthio, alkylthioalkyl,
 110 alkylamino, trialkylsilyl,
 $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl,
 $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl,
 $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl; and
 $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl; and

115 when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is
 hydroxy, and R_5 is hydrogen, then R_6 is selected from the
 group consisting of hydroxy, alkyl, fluorinated alkyl,
 alkoxy, alkoxyalkyl and alkoxycarbonyl; and

when R_2 is trifluoromethyl, R_3 is selected from the
 120 group consisting of $-\text{CO}_2\text{H}$ and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is methyl, and R_6
 is selected from the group consisting of hydrogen and
 trifluoromethyl, then R_4 is selected from the group
 consisting of hydrogen, halogen, alkyl, cycloalkyl,
 haloalkyl, alkenyl, aryl, heteroaryl, cycloalkylalkyl,
 125 heteroarylalkyl, aralkenyl, alkoxy, aralkoxy,
 alkoxycarbonyl, arylcarbonyloxy, thio, alkylthio,
 arylthio, cycloalkylthio, heterocyclylthio,
 alkylthioalkyl, alkylamino, trialkylsilyl,
 $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl,
 130 $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl,

245

-OP(O) (OR₁₀)₂, wherein R₁₀ is alkyl, and

-OP(S) (OR₁₁)₂, wherein R₁₁ is alkyl.

4. The method of claim 2 wherein:

R₂ is selected from the group consisting of methyl and fluorinated methyl; and

R₃ is -CO₂R₇, wherein R₇ is selected from the group
5 consisting of hydrogen, methyl and ethyl.

5. The method of claim 2 wherein:

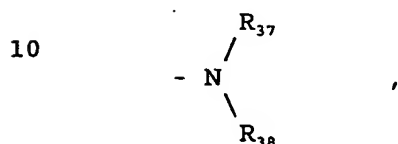
R₂ is fluorinated alkyl;

R₃ is -CO₂R₇, wherein R₇ is selected from the group
consisting of hydrogen and alkyl;

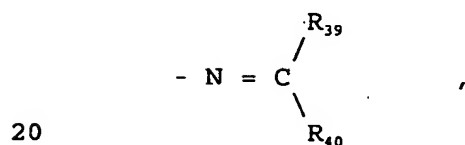
5 R₄ is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl;

R₅ is selected from the group consisting of:

pyrrolyl;



15 wherein R₃₇ and R₃₈ are independently alkyl;



wherein R₃₉ is selected from the group
consisting of hydrogen, alkoxy, and alkylthio, and

246

25 R_{40} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

- $N = R_{41}$,

wherein R_{41} is heterocyclidenyl;

30 $-NR_{42} - \overset{\overset{O}{\parallel}}{C} - R_{43}$,

wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and

R_{43} is selected from the group consisting of cycloalkyl, chlorinated alkyl, and heteroaryl;

35 $-NH - \overset{\overset{O}{\parallel}}{C} - NH - R_{44}$,
wherein R_{44} is heteroaryl;

- $N = S = O$;

40 - $N = C = S$;

- $N = C = O$; and

- N_3 ; and

R_6 is fluorinated alkyl;

45 or a pharmaceutically acceptable salt or tautomer thereof.

6. The method of claim 2 wherein:

R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

5 R_4 is selected from the group consisting of alkyl, haloalkyl, cycloalkyl, alkoxy and alkylthio;

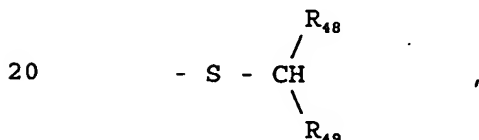
R_5 is selected from the group consisting of:

- SR_{45} ,

10 wherein R_{45} is selected from the group consisting of hydrogen, alkyl, haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, aminocarbonylalkyl, alkylthioalkyl, $-\text{SR}_{46}$, and $-\text{CH}_2R_{47}$,

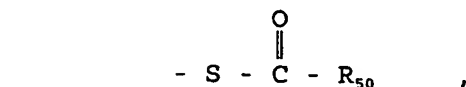
15 wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and

R_{47} is selected from the group consisting of aryl and heteroaryl; and



wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

25 R_{49} is selected from the group consisting of alkoxy and haloalkyl;



wherein R_{50} is selected from the group

consisting of alkyl, alkoxy, aryl and heteroaryl;

35
$$\begin{array}{c} \text{O} \\ || \\ - \text{S} - \text{R}_{51} \end{array},$$
 wherein R_{51} is selected from the group consisting of alkyl and haloalkyl; and

40
$$\begin{array}{c} \text{O} \\ || \\ - \text{S} - \text{R}_{53} \\ || \\ \text{O} \end{array},$$
 wherein R_{53} is aryl; and

R_6 is fluorinated alkyl;

45 or a pharmaceutically acceptable salt or tautomer thereof.

7. The method of claim 2 wherein:

R_2 is selected from the group consisting of alkyl and fluorinated alkyl;

5 R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of hydroxy, alkoxy, aralkoxy, alkoxycarbonyl, alkylthio, arylthio, $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl, $-\text{SO}_2\text{R}_9$, wherein R_9 is aryl, $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_{10} is alkyl, and $-\text{OP}(\text{S})(\text{OR}_{11})_2$, wherein R_{11} is alkyl;

10

R_5 is selected from the group consisting of hydrogen, hydroxy, halogen, alkoxy, and aryloxy; and

R_6 is selected from the group consisting of hydrogen,
 15 fluorinated alkyl and alkoxy carbonyl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_2 is trifluoromethyl, R_3 is
 $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydroxy and R_5 is hydrogen, then R_6 is
 20 selected from the group consisting of fluorinated alkyl
 and alkoxy carbonyl.

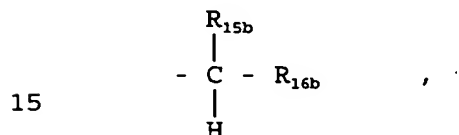
8. The method of claim 2 wherein:

R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group
 consisting of hydrogen, alkyl and cyanoalkyl;

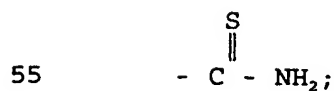
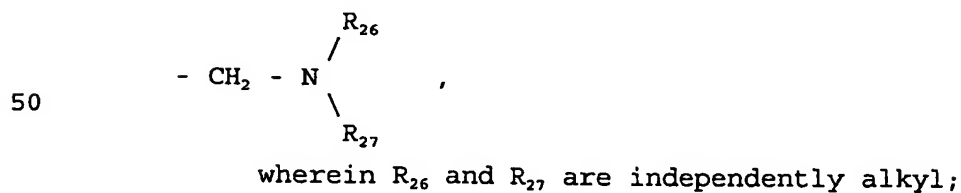
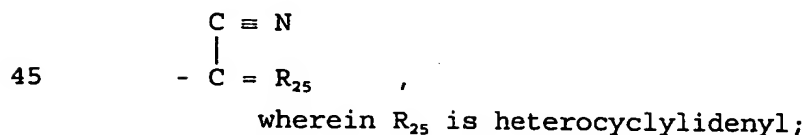
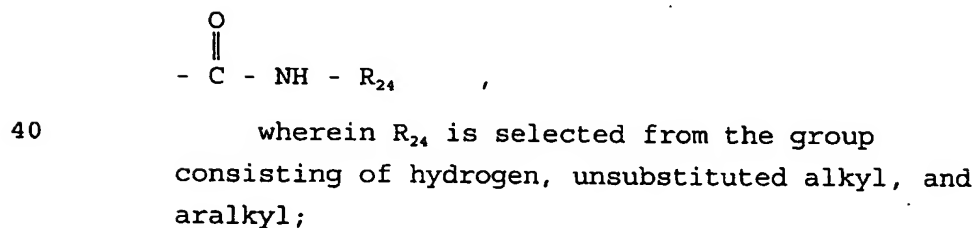
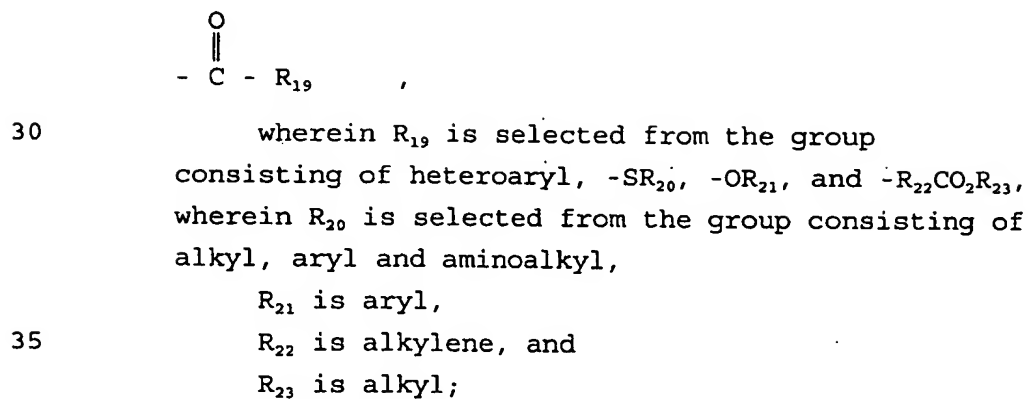
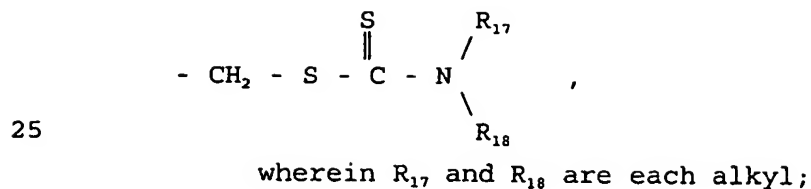
5 R_4 is selected from the group consisting of alkyl,
 alkoxy, cycloalkyl, cycloalkylalkyl, arylcarbonyloxy,
 arylthio, and alkylamino;

R_5 is selected from the group consisting of alkyl,
 haloalkyl, alkynyl, heterocyclyl, heteroaryl,
 10 heterocyclylalkyl, arylcarbonyloxyalkyl, alkylthioalkyl,
 arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, cyano,

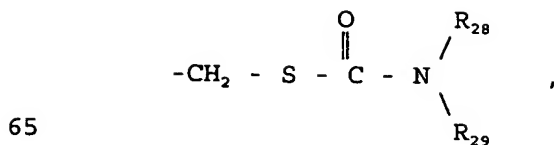
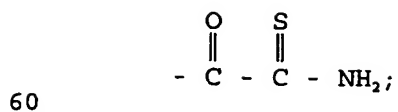


wherein R_{15b} is selected from the group
 consisting of hydroxy, alkylthio and alkoxy, and
 R_{16b} is selected from the group consisting of
 20 alkyl and heteroaryl;

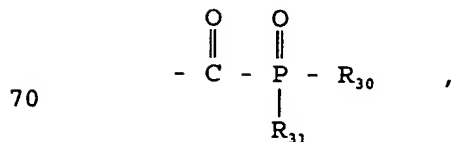
250



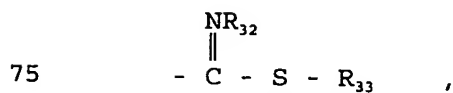
251



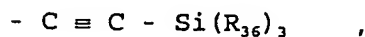
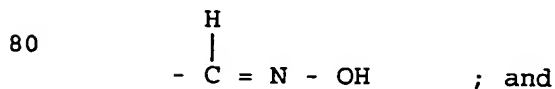
wherein R_{28} and R_{29} are independently alkyl;



wherein R_{30} and R_{31} are each alkoxy;



wherein R_{32} is selected from the group consisting of hydrogen and alkyl, and R_{33} is alkyl;



wherein R_{36} is alkyl; and

85 R_6 is selected from the group consisting of hydrogen, fluorinated alkyl and alkoxy,

or a pharmaceutically acceptable salt or tautomer thereof,

252

provided that:

90

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is $-\overset{\text{O}}{\parallel}\text{C}-R_{19}$, R_6 is trifluoromethyl, and R_{19} is the heteroaryl 1-pyrazolyl, then R_4 is selected from the group consisting
95 of alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, arylcarbonyloxy, and arylthio; and

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_5 is the heterocyclyl 2-(4,5-dihydro-oxazolyl), and R_6 is trifluoromethyl, then R_4 is selected from the group
100 consisting of alkyl, alkoxy, cycloalkyl, arylcarbonyloxy, arylthio, and alkylamino; and

when R_2 and R_6 are independently fluorinated methyl, R_3 is $-\text{CO}_2R_7$, R_5 is cyano, and R_7 is selected from the group consisting of hydrogen and alkyl, then R_4 is
105 selected from the group consisting of alkoxy, cycloalkyl, cycloalkylalkyl, arylcarbonyloxy, arylthio, and alkylamino.

9. The method of claim 2 wherein:

R_2 is selected from the group consisting of hydroxy, alkyl, fluorinated alkyl, and alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy, amido, and $-\text{CO}_2R_7$, wherein R_7 is selected from the group
5 consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of hydrogen, hydroxy, halogen, alkyl, cycloalkyl, haloalkyl, alkenyl, aryl, heteroaryl, heteroarylalkyl, alkoxy,
10 alkoxycarbonyl, aralkenyl, thio, alkylthio, cycloalkylthio, heterocyclylthio, alkylthioalkyl, and

trialkylsilyl;

R_5 is CO_2R_{14} , wherein R_{14} is alkyl;

15 R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, and alkoxyalkyl,

or a pharmaceutically acceptable salt or tautomer thereof,

provided that,

20 when R_2 is methyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is alkoxy, and R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl comprising at least two carbon atoms, fluorinated alkyl, and alkoxyalkyl,

25 when R_2 is difluoromethyl, R_3 is $-\text{CO}_2R_7$, R_4 is alkenyl, R_5 is CO_2CH_3 , and R_6 is trifluoromethyl, R_7 is alkyl,

30 when R_2 is methyl, R_4 is hydrogen, R_5 is CO_2R_{14} , R_6 is methyl, and R_{14} is alkyl, R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms and cyanoalkyl,

35 when R_2 is difluoromethyl, R_4 is hydrogen, R_5 is CO_2R_{14} , R_6 is trifluoromethyl, and R_{14} is alkyl, R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen, methyl, alkyl comprising at least three carbon atoms and cyanoalkyl,

when R_2 is difluoromethyl, R_4 is alkylthioalkyl, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is methyl, R_3 is selected from the group consisting of hydroxy, amido and $-\text{CO}_2\text{R}_7$, wherein R_7 is alkyl, and

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{CH}_3$, R_4 is alkyl, and R_5 is $-\text{CO}_2\text{CH}_3$, R_6 is selected from the group consisting of hydrogen, hydroxy, alkyl comprising two or more carbon atoms, fluorinated alkyl, and alkoxyalkyl; and

when R_2 is difluoromethyl, R_4 is alkyl, R_5 is selected from the group consisting of $-\text{CO}_2\text{CH}_3$ and $-\text{CO}_2\text{C}_2\text{H}_5$, and R_6 is trifluoromethyl, R_3 is selected from the group consisting of hydroxy and $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl.

10. The method of claim 2 wherein the compound of formula IA is selected from the compounds and pharmaceutically acceptable salts and tautomers thereof of the group consisting of:

Methyl 5-[(4-t-Butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-(methoxycarbonylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Diethyl 2,6-Bis(trifluoromethyl)-4-(trimethylsilyl)-3,5-pyridinedicarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(methylthiomethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

20 Methyl 5-(1-Bromo-2-methoxyethenyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-(Chloroethylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

25 Methyl 4-(i-Propoxy)-5-{[3-(methoxycarbonyl)-4-(i-propoxy)-6-(trifluoromethyl)-5-pyridyl]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-cyclobutyl-5-(1-pyrrolyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

30 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(aminothionocarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(dimethylamino)carbonyl]thiomethyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

35 Methyl 2-(Difluoromethyl)-5-[(diethylphosphono)carbonyl]-4-(i-propylamino)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Dimethyl 2,6-Bis(methoxymethyl)-4-propyl-3,5-pyridinecarboxylate;

40 Methyl 5-[(Aminocarbonyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2- (Difluoromethyl) -5- (1-ethoxyethylthio) -4-
(2-methylpropyl) -6- (trifluoromethyl) -3-pyridine-
45 carboxylate;

Methyl 2- (Difluoromethyl) -4- (2-methylpropyl) -5-
(1-methoxyethylthio) -6- (trifluoromethyl) -3-
pyridinecarboxylate;

Methyl 2- (Difluoromethyl) -5- (2-fluoroethylthio) 4-
50 (2-methylpropyl) -6- (trifluoromethyl) -3-pyridine-
carboxylate;

Methyl 5- (Acetylthio) -2- (difluoromethyl) -4-
(2-methylpropyl) -6- (trifluoromethyl) -3-pyridine-
carboxylate;

55 Methyl 2- (Difluoromethyl) -4- (2-methylpropyl) -5-
(2-tetrahydrofurylthio) -6- (trifluoromethyl) -3-
pyridinecarboxylate;

Methyl 2- (Difluoromethyl) -5- { [(3,5-di-t-butylphenyl)
thio] carbonyl } -4- (2-methylpropyl) -6- (trifluoromethyl) -3-
60 pyridinecarboxylate;

Methyl 2- (Difluoromethyl) -5- { [(2,4-dimethylphenyl)
thio] carbonyl } -4- (2-methylpropyl) -6- (trifluoromethyl) -3-
pyridinecarboxylate;

Methyl 2- (Difluoromethyl) -4- (2-methylpropyl) -5-
65 { [(2-methoxyphenyl) thio] carbonyl } -6- (trifluoromethyl) -3-
pyridinecarboxylate;

Methyl 2- (Difluoromethyl) -4- (2-methylpropyl) -5-
{ [(3-methoxyphenyl) thio] carbonyl } -6- (trifluoromethyl) -3-
pyridinecarboxylate;

70 Methyl 2-(Difluoromethyl)-5-{{(2,4-di-t-butylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-{{(4-t-Butylphenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
75 3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-isopropylphenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-{{(3,5-dimethylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;
80

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(4-methylthiophenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

85 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-(4-fluorobenzyl)-4-isopropylphenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-(4-fluorobenzyl)-4-fluorophenyl)thio}carbonyl}-6-
90 (trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-{{(4-chlorophenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-{{(2,5-Dichlorophenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
95 3-pyridinecarboxylate;

Methyl 5-{[(2,6-Dichlorophenyl)thio]carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

100 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(2-naphthyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{[(1-naphthyl)thio]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

105

3-Methyl 5-(3-Methoxyphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

3-Methyl 5-(2-Nitrophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

110

3-Methyl 5-(3,5-Di-t-butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

3-Methyl 5-(2,4-Di-t-butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

115

3-Methyl 5-(4-t-Butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

120

3-Methyl 5-[2-(4-Fluorobenzyl)-4-isopropylphenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

125 3-Methyl 5-[2-(4-Fluorobenzyl)-3,4,5-(trimethoxy)
phenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-
(trifluoromethyl)-3,5-pyridicarboxylate;

3-Methyl 5-(2-Methoxyphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate;

130 3-Methyl 5-(4-Chlorophenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate;

135 3-Methyl 5-(3,5-Dimethylphenyl) 2-(Difluoromethyl)-
4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate;

3-Methyl 5-(2-Isopropylphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate;

140 3-Methyl 5-(2,6-Dimethyl-4-nitrophenyl) 2-
(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3,5-pyridicarboxylate;

3-Methyl 5-(2,4-Dimethylphenyl) 2-(Difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-
pyridicarboxylate;

145 Methyl 5-(4-t-Butylphenyldithio)-2-(difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate;

150 Dimethyl 5,5'-Dithiobis[2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3-pyridine-
carboxylate;

Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]methylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

155 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]carbonylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

160 Methyl 5-[(3-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(4-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

165 Methyl 5-[(2,3,5,6-Tetrafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

170 Methyl 5-[(3,5-Di-t-butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(1-Methylimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

175 Methyl 5-[(1-Methyltetrazol-5-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(5-Nitrobenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

180 Methyl 5-[(4-(Trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Quinolin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

185

Methyl 5-[(4-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Pentafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

190

Methyl 5-[(2,5-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

195

Methyl 5-[(4-Methylpyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

200

Methyl 5-[(4-Nitrophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

205 Methyl 5-[(4-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

210 Methyl 5-[(2,6-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

215 Methyl 5-[(Quinolin-8-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Pyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

220 Methyl 5-[(4-(Acetylamino)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Benzoxazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

225 Methyl 5-[(4-Bromo-2-(trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

230 Methyl 5-[(3-Aminophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

235 Methyl 5-[(5-Methylbenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Benzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

240 Methyl 5-[(3-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

245 Methyl 5-[(Benzothiazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(3-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

250 Methyl 5-[(3,4-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-Naphthyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

255 Methyl 5-[(2-Pyridyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

264

Methyl 5-[(2-bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

260

Bis{3-(carbomethoxy)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-5-pyridyl}methyl Sulfide;

Methyl 5-[(2-Chloro-3,4-methylenedioxyphenyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

265

Methyl 5-[(2-pyridyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-quinolinyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

270

Methyl 5-[(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate; and

275

Methyl 5[(6-chloro-1,3-benzodioxan-8-yl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Diethyl 5,5'-(Carbonyldiimino)bis[6(difluoromethyl)-4-ethyl-2-(trifluoromethyl)-3-pyridinecarboxylate;

280

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[[(dimethylamino)thiono]thiomethyl]-6-(trifluoromethyl)-3-pyridinecarboxylate;

265

285 2- (Difluoromethyl) -5-hydroxymethyl-4-phenyl-6-
(trifluoromethyl) -3- { [4- (trifluoromethyl)phenyl]
hydroxymethyl}pyridine;

2- (Difluoromethyl) -5-hydroxymethyl-4-phenyl-6-
(trifluoromethyl) -3- { [4- (trifluoromethyl)phenyl]
carbonyl}pyridine;

290 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

295 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl)phenyl]carbonyl}pyridine;

2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl)phenyl]fluoromethyl}pyridine;

300 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl)phenyl]fluoromethyl}pyridine;

2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- (2-
naphthylfluoromethyl)pyridine;

305 2- (Difluoromethyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl)phenyl]mercaptomethyl}pyridine;

310 2- (Difluoromethyl) -5-hydroxymethyl-4-phenyl-6-
(trifluoromethyl) -3- { [4- (trifluoromethyl)phenyl]
mercaptomethyl}pyridine;

266

2- (Cyclopentyl) -5-hydroxymethyl-4- (4-fluorophenyl) -
6- (trifluoromethyl) -3- { [4- (trifluoromethyl) phenyl]
carbonyl} pyridine;

315 2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] carbonyl} pyridine;

2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] hydroxymethyl} pyridine; and

320 2- (1-Pyrrolidinyl) -5-hydroxymethyl-4- (4-
fluorophenyl) -6- (trifluoromethyl) -3- { [4-
(trifluoromethyl) phenyl] fluoromethyl} pyridine.

11. The method of claim 2 wherein

R_2 is selected from the group consisting of alkyl and
fluorinated alkyl;

5 R_3 is selected from the group consisting of $-CO_2R_7$,
wherein R_7 is selected from the group consisting of
hydrogen and alkyl;

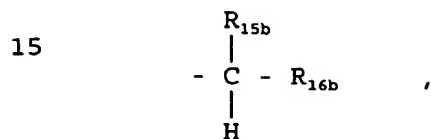
R_4 is selected from the group consisting of alkyl,
cycloalkyl, arylcarbonyloxy, thio, arylthio, and
heterocyclylthio,

10 R_5 is selected from the group consisting of alkyl,
heterocyclyl, arylthioalkyl, heteroarylthioalkyl,

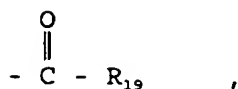
$-CO_2R_{14}$,

wherein R_{14} is alkyl;

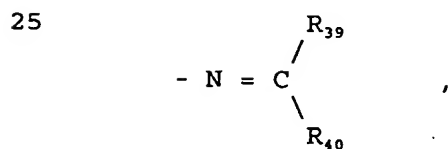
267



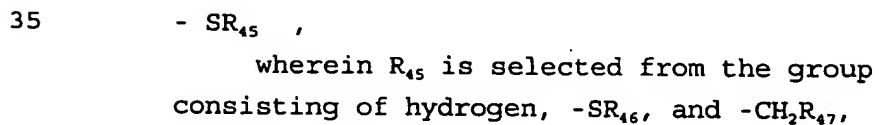
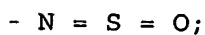
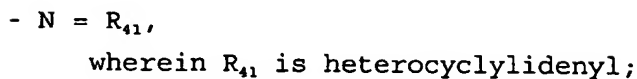
20 wherein R_{15b} is hydroxy, and
 R_{16b} is heteroaryl;



 wherein R_{19} is $-\text{SR}_{20}$, and R_{20} is alkyl;

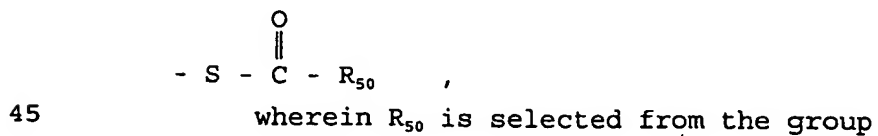


30 wherein R_{39} is alkoxy, and
 R_{40} is haloalkyl;



 wherein R_{46} is selected from the group
 consisting of aryl and heteroaryl, and

40 R_{47} is selected from the group consisting of
 aryl and heteroaryl; and



268

consisting of alkyl and alkoxy;

R₆ is selected from the group consisting of alkyl and fluorinated alkyl.

50 or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R₂ is trifluoromethyl, R₃ is CO₂CH₃, R₄ is isobutyl, and R₅ is -CO₂CH₃, then R₆ is selected from the group consisting of alkyl comprising at least two carbon atoms and fluorinated alkyl.

12. The method of claim 2 wherein the compound of formula IA is selected from the compounds and pharmaceutically acceptable salts and tautomers thereof of the group consisting of:

5 Methyl 5-(4-t-Butylphenyldithio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

10 Dimethyl 5,5'-Dithiobis[2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(3,4-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

15 Methyl 2-(Difluoromethyl)-5-isothiocyanato-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-Naphthyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

20 Methyl 2-(Difluoromethyl)-5-mercapto-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

5-Ethyl 3-Methyl 2-(Difluoromethyl)-4-[(4,5-dihydro-2-thiazolyl)thio]-6-(trifluoromethyl)-3,5-pyridine-
25 dicarboxylate;

Methyl 5-[(4-Nitrophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-(methoxycarbonylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

35 Methyl 5-[(4-t-Butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-[(1,4-dithian-2-ylidene)amino]-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

40 Methyl 5-[(4-(Trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

45 Methyl 5-[(4-Chlorophenyl)thiomethyl]-2-(difluoro-
methyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
pyridinecarboxylate;

Methyl 5-[(5-Methylbenzimidazol-2-yl)thiomethyl]-
2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoro-
methyl)-3-pyridinecarboxylate;

50 Methyl 5-[(Benzothiazol-2-yl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

Methyl 5-[(3-Chlorophenyl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
55 3-pyridinecarboxylate;

Methyl 5-{[3-(Carbomethoxy)-2-(difluoromethyl)-4-
isobutyl-6-(trifluoromethyl)-5-pyridyl]thiomethyl}-2-
(difluoromethyl)-4-isobutyl-6-(trifluoromethyl)-3-
pyridinecarboxylate;

60 Di-t-Butyl 2-(difluoromethyl)-4-(2-methylpropyl)-6-
(trifluoromethyl)-3,5-pyridinedicarboxylate;

Methyl 5-[(4-Bromophenyl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

65 Methyl 5-[(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)
phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-
6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(4-Methoxyphenyl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
70 3-pyridinecarboxylate;

271

Methyl 5-[(Benzoxazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

75 Methyl 5-[(Benzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(4,5-dihydro-2-thiazoyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

80 Ethyl 2,6-Bis(trifluoromethyl)-5-methyl-4-[4-(trifluoromethylphenyl)carbonyloxy]-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-[(i-propylthio)carbonyl]-4-(cyclobutyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

85 Methyl 4-(4-i-Propylphenylthio)-5-methyl-6-(trifluoromethyl)-3-pyridinecarboxylate;

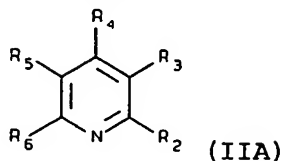
Methyl 5-[(5-Nitrobenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate; and

90 Bis {[3-(carbomethoxy)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-5-pyridyl]methyl Sulfide.

13. The method of claim 2 wherein the compound of formula IA is Dimethyl 5,5'-dithiobis[2-difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate].

272

14. A compound represented by the generic formula:



wherein:

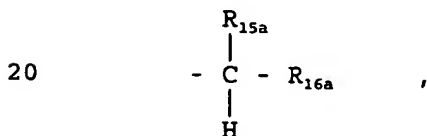
R_2 and R_6 are independently selected from the group
 5 consisting of hydrogen, hydroxy, alkyl, fluorinated
 alkyl, fluorinated aralkyl, chlorofluorinated alkyl,
 cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy,
 alkoxyalkyl, and alkoxy carbonyl; provided that at least
 one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated
 10 alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of
 arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,
 arylalkoxyalkyl, trialkylsilyloxyalkyl,

-CHO,

15 -CO₂R₇,

wherein R₇ is selected from the group consisting
 of hydrogen and alkyl; and



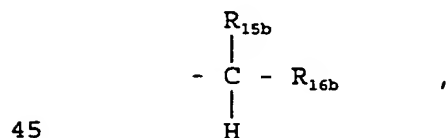
wherein R_{15a} is selected from the group
 consisting of hydroxy, halogen, alkylthio and
 25 alkoxy, and

R_{16a} is selected from the group consisting of
 alkyl, haloalkyl, alkenyl, aryl and heteroaryl;

30 R_4 is selected from the group consisting of hydrogen, hydroxy, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, alkoxy, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl;

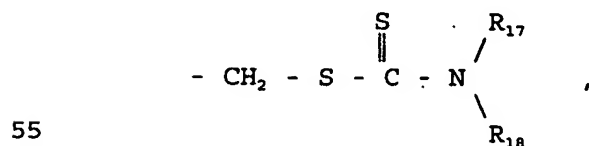
R₅ is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aralkyl, alkoxy, aryloxy, cycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, arylcarbonyloxyalkyl, pyrrolyl, substituted pyrrolidinyl, hydroxymethyl, arylalkoxyalkyl, and trialkylsilyloxyalkyl,

40 - CO₂R₁₄,
 wherein R₁₄ is alkyl;

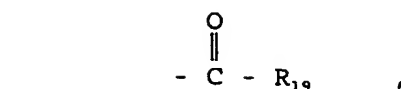


wherein R_{15b} is selected from the group consisting of hydroxy, halogen, alkoxy, and alkylthio, aryloxy, and alkylsulfonyloxy, and

50 R_{16b} is selected from the group consisting of alkyl, alkenyl, aryl, and heteroaryl;



wherein R_{17} and R_{18} are independently alkyl;



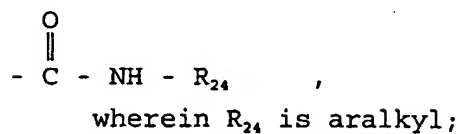
60 wherein R₁₉ is aryl, heteroaryl, -SR₂₀, and -OR₂₁,

274

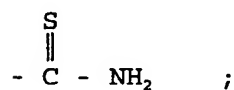
wherein R_{20} is selected from the group consisting of aryl, heteroaryl and aminoalkyl, and

R_{21} is selected from the group consisting of aryl and heteroaryl;

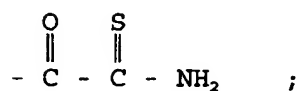
65



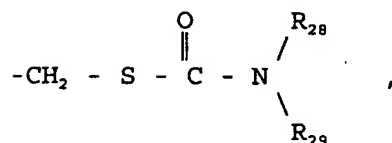
70



75

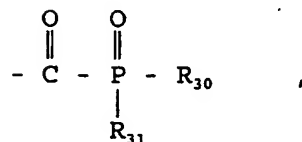


80

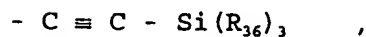


wherein R_{28} and R_{29} are independently alkyl;

85



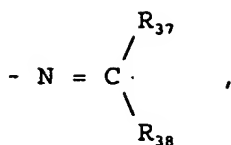
wherein R_{30} and R_{31} are independently alkoxy;



wherein R_{36} is alkyl;

275

90



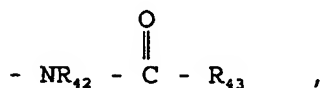
95

wherein R_{37} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

100

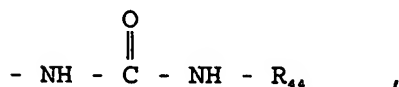
provided that when R_{37} is hydrogen, then R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclalkoxy;

105

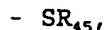


wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and R_{43} is substituted heteroaryl;

110



wherein R_{44} is selected from the group consisting of aryl and heteroaryl;



115

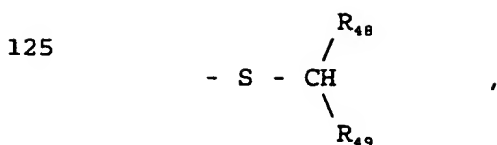
wherein R_{45} is selected from the group consisting of haloalkyl, heterocyclalkyl, alkylthioalkyl, aminocarbonylalkyl, $-SR_{46}$, and $-CH_2R_{47}$,

120

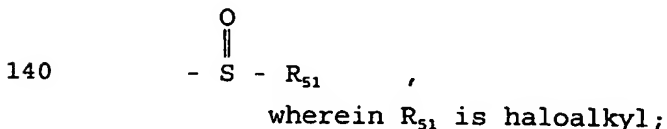
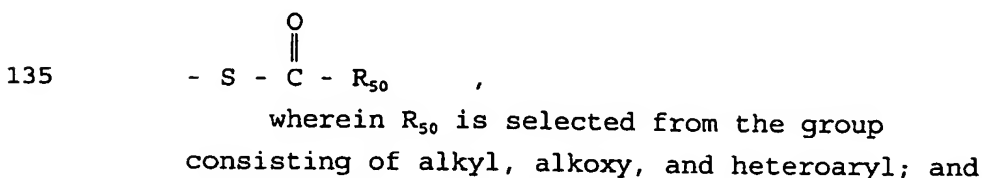
wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and

R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, tetrahydronaphthyl and benzodioxanyl;

276



130 wherein R_{48} is selected from the group
consisting of hydrogen and alkyl, and
 R_{49} is selected from the group consisting of
alkoxy and haloalkyl;



or a pharmaceutically acceptable salt or tautomer
thereof,

provided that:

145 when R_2 is selected from the group consisting of
difluoromethyl and trifluoromethyl, R_3 is selected from
the group consisting of $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, and $-\text{CO}_2\text{C}_2\text{H}_5$, R_5 is
hydrogen, and R_6 is selected from the group consisting of
hydrogen and trifluoromethyl, then R_4 is selected from the
150 group consisting of cycloalkyl, cycloalkylalkyl,
heteroarylalkyl, aralkenyl, alkoxy, thio, trialkylsilyl,
alkylamino, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl;
provided further that when R_2 , R_3 and R_5 are as defined
above, and R_4 is alkoxy, then R_6 is hydrogen;

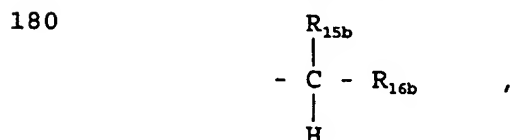
155 when R_2 is selected from the group consisting of

fluorinated methyl and chlorofluorinated methyl, R_3 is selected from the group consisting of hydroxymethyl and CO_2R_7 , R_5 is selected from the group consisting of hydroxymethyl and CO_2R_{14} , R_6 is selected from the group consisting of fluorinated methyl and chlorofluorinated methyl, and R_7 and R_{14} are independently alkyl, then R_4 is selected from the group consisting of thio, trialkylsilyl, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl;

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydrogen, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is selected from the group consisting of hydrogen, monofluoroalkyl, difluoroalkyl and alkoxyalkyl;

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2R_7$, R_5 is methyl, R_6 is selected from the group consisting of fluorinated methyl, fluorinated ethyl and chlorofluorinated methyl, and R_7 is selected from the group consisting of hydrogen and alkyl, then R_4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl;

when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_3 is $-\text{CO}_2R_7$, and R_7 is alkyl, then R_5 is other than arylcarbonyl, heteroarylcarbonyl or



185 wherein R_{16b} is alkyl when R_{15b} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16b} is aryl or heteroaryl when R_{15b} is hydroxy;

when R_4 is selected from the group consisting of

alkyl, cycloalkyl and cycloalkylalkyl, R_5 is $-\text{CO}_2R_{14}$, and
 190 R_{14} is alkyl, then R_3 is other than arylcarbonyl,
 heteroarylcarbonyl or



wherein R_{16a} is alkyl when R_{15a} is selected from the group
 consisting of hydroxy, halogen, alkylthio and alkoxy, or
 wherein R_{16a} is aryl or heteroaryl when R_{15a} is hydroxy; and

200 when R_2 and R_6 are independently selected from
 fluorinated methyl and chlorofluorinated methyl, R_3 is
 CO_2R_7 , R_5 is hydroxy, alkoxy or aryloxy, then R_4 is
 selected from the group consisting of aryl, cycloalkyl,
 cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl,
 205 alkylamino, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl; and

when R_4 is aryl and one of R_2 and R_6 is
 trifluoromethyl, then the other of R_2 and R_6 is
 difluoromethyl.

15. A compound of claim 14 wherein:

R_2 is fluorinated methyl; and

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group
 consisting of hydrogen, methyl and ethyl.

16. A compound of claim 14 wherein:

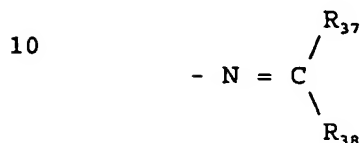
R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group
 consisting of hydrogen and alkyl;

5 R_4 is selected from the group consisting of alkyl and
 cycloalkyl;

R₅ is selected from the group consisting of:

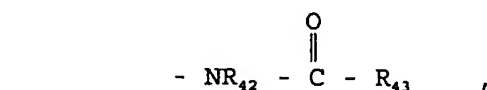
1-pyrrolyl;



15 wherein R₃₇ is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and

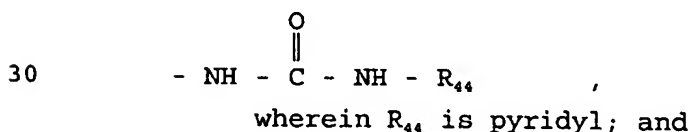
 R₃₈ is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

20 provided that when R₃₇ is hydrogen, then R₃₈ is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclalkoxy;



 wherein R₄₂ is selected from the group consisting of hydrogen and alkyl, and

 R₄₃ is substituted heteroaryl;



R₆ is fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof.

17. A compound of claim 14 wherein:

R₂ is fluorinated alkyl;

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

5 R_4 is alkyl;

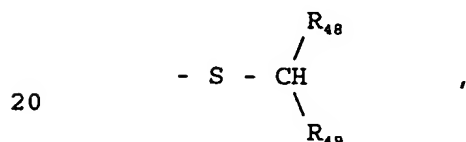
R_5 is selected from the group consisting of:

- SR_{45}

10 wherein R_{45} is selected from the group consisting of haloalkyl, heterocyclyl, aralkyl, heteroaralkyl, alkylthioalkyl, aminocarbonylalkyl, - SR_{46} , and $-\text{CH}_2R_{47}$,

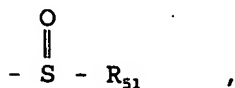
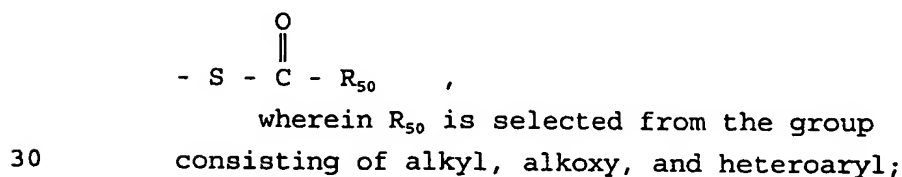
wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and

15 R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, tetrahydronaphthyl and benzodioxanyl; and



wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and

25 R_{49} is selected from the group consisting of alkoxy and haloalkyl;



wherein R_{51} is haloalkyl; and

35 R_6 is fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof.

18. A compound of claim 14 wherein:

R_2 is fluorinated alkyl;

R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

5 R_4 is hydroxy, alkoxy, $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, or $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_8 is aryl and R_{10} is alkyl;

R_5 is selected from the group consisting of hydrogen, alkoxy and aryloxy; and

10 R_6 is selected from the group consisting of hydrogen and fluorinated alkyl;

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_2 is trifluoromethyl, R_3 is selected from the group consisting of $-\text{CO}_2\text{CH}_3$ and $-\text{CO}_2\text{C}_2\text{H}_5$,
15 R_5 is hydrogen, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is selected from the group consisting of alkoxy, $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, or $-\text{OP}(\text{O})(\text{OR}_{10})_2$, wherein R_8 is aryl and R_{10} is alkyl; provided further that when R_2 , R_3 and R_5 are as
20 defined above, and R_4 is alkoxy, then R_6 is hydrogen.

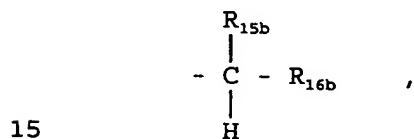
19. A compound of claim 14 wherein:

R_2 is fluorinated alkyl;

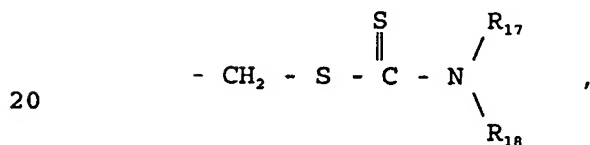
R_3 is $-\text{CO}_2R_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

5 R_4 is selected from the group consisting of alkyl, alkoxy, cycloalkyl, cycloalkylalkyl, arylthio, and alkylamino; and

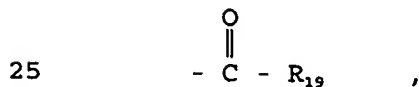
R_5 is selected from the group consisting of alkyl, arylcarbonyloxyalkyl, arylthioalkyl, heteroarylthioalkyl,
10 alkoxyalkenyl, substituted pyrrolidinyl,



wherein R_{15b} is alkoxy, and R_{16b} is heteroaryl;

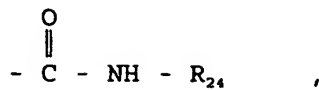


wherein R_{17} and R_{18} are independently alkyl;



wherein R_{19} is selected from the group consisting of pyridyl, $-\text{SR}_{20}$, and $-\text{OR}_{21}$, wherein R_{20} is selected from the group consisting of aryl, heteroaryl and aminoalkyl, and R_{21} is selected from
30 the group consisting of aryl and heteroaryl;

283

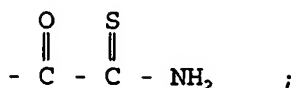


wherein R_{24} is aralkyl;

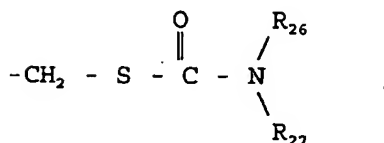
35



40

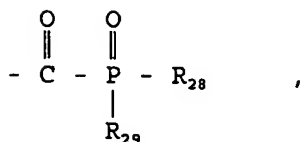


45



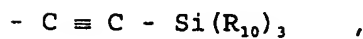
wherein R_{26} and R_{27} are independently alkyl;

50



wherein R_{28} and R_{29} are independently alkoxy; and

55



wherein R_{10} is alkyl; and

R_6 is selected from the group consisting of hydrogen and fluorinated alkyl,

60

or a pharmaceutically acceptable salt or tautomer

thereof,

provided that:

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is isopropoxy, R_5 is methyl, then R_6 is hydrogen; and

65 when R_5 is alkyl, then R_4 is selected from the group consisting of cycloalkyl, cycloalkylalkyl, arylthio, and alkylamino.

20. A compound of claim 14 wherein:

R_2 is selected from the group consisting of fluorinated alkyl and alkoxyalkyl;

5 R_3 is $-\text{CO}_2\text{R}_7$, wherein R_7 is selected from the group consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of hydrogen, hydroxy, alkyl, heteroarylalkyl, thio, and trialkylsilyl;

R_5 is CO_2R_{14} , wherein R_{14} is alkyl; and

10 R_6 is selected from the group consisting of hydrogen, fluorinated alkyl, and alkoxyalkyl,

or a pharmaceutically acceptable salt or tautomer thereof,

provided that when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydrogen, R_5 is $\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is selected
15 from the group consisting of hydrogen, monofluoroalkyl, and difluoroalkyl.

21. A compound of claim 14 selected from compounds and their pharmaceutically acceptable salts and tautomers of the group consisting of:

5 Methyl 5-[(4-t-Butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(palmitoylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

10 Methyl 2-(Difluoromethyl)-5-(methoxycarbonylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Diethyl 2,6-Bis(trifluoromethyl)-4-(trimethylsilyl)-3,5-pyridinedicarboxylate;

15 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(methylthiomethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

20 Methyl 5-(1-Bromo-2-methoxyethenyl)-4-(cyclopropylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-(Chloroethylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

25 Methyl 4-(i-Propoxy)-5-{[3-(methoxycarbonyl)-4-(i-propoxy)-6-(trifluoromethyl)-5-pyridyl]carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-cyclobutyl-5-(1-pyrrolyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(aminothionocarbonyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

30

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[[(dimethylamino) carbonyl]thiomethyl]-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-[(diethylphosphono) carbonyl]-4-(i-propylamino)-6-(trifluoromethyl)-3-pyridinecarboxylate;

35

Dimethyl 2,6-Bis(methoxymethyl)-4-propyl-3,5-pyridinecarboxylate;

Methyl 5-[(Aminocarbonyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

40

Methyl 2-(Difluoromethyl)-5-(1-ethoxyethylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(1-methoxyethylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

45

Methyl 2-(Difluoromethyl)-5-(2-fluoroethylthio)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

50

Methyl 5-(Acetylthio)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

55 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-(2-tetrahydrofurylthio)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-5-{{(3,5-di-t-butylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

60 Methyl 2-(Difluoromethyl)-5-{{(2,4-dimethylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

65 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-methoxyphenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(3-methoxyphenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

70 Methyl 2-(Difluoromethyl)-5-{{(2,4-di-t-butylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-{{(4-t-Butylphenyl)thio}carbonyl}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

75 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-{{(2-isopropylphenyl)thio}carbonyl}-6-(trifluoromethyl)-3-pyridinecarboxylate;

80 Methyl 2-(Difluoromethyl)-5-{{(3,5-dimethylphenyl)thio}carbonyl}-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(4-methylthiophenyl)thio]carbonyl}-6-(trifluoromethyl)-
3-pyridinecarboxylate;

85 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(2-(4-fluorobenzyl)-4-isopropylphenyl)thio]carbonyl}-6-
(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(2-(4-fluorobenzyl)-4-fluorophenyl)thio]carbonyl}-6-
(trifluoromethyl)-3-pyridinecarboxylate;

90 Methyl 5-{[(4-chlorophenyl)thio]carbonyl}-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
-pyridinecarboxylate;

Methyl 5-{[(2,5-Dichlorophenyl)thio]carbonyl}-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
95 -pyridinecarboxylate;

Methyl 5-{[(2,6-Dichlorophenyl)thio]carbonyl}-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-
-pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
100 {[(2-naphthyl)thio]carbonyl}-6-(trifluoromethyl)-3-
pyridinecarboxylate;

Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-
{[(1-naphthyl)thio]carbonyl}-6-(trifluoromethyl)-3-
pyridinecarboxylate;

105 3-Methyl 5-(3-Methoxyphenyl) 2-(Difluoromethyl)-4-
(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridi-
carboxylate;

110 3-Methyl 5-(2-Nitrophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

3-Methyl 5-(3,5-Di-*t*-butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

115 3-Methyl 5-(2,4-Di-*t*-butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

3-Methyl 5-(4-*t*-Butylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

120 3-Methyl 5-[2-(4-Fluorobenzyl)-4-isopropylphenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

125 3-Methyl 5-[2-(4-Fluorobenzyl)-3,4,5-(trimethoxy)phenyl] 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

3-Methyl 5-(2-Methoxyphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

130 3-Methyl 5-(4-Chlorophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

3-Methyl 5-(3,5-Dimethylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

135 3-Methyl 5-(2-Isopropylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

 3-Methyl 5-(2,6-Dimethyl-4-nitrophenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
140 3,5-pyridinecarboxylate;

 3-Methyl 5-(2,4-Dimethylphenyl) 2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate;

 Methyl 5-(4-*t*-Butylphenyl)dithio-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;
145

 Dimethyl 5,5'-Dithiobis[2-(Difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate];

150 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]methylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

 Methyl 5-{[2-(Difluoromethyl)-4-(2-methylpropyl)-3-(methoxycarbonyl)-6-(trifluoromethyl)-5-pyridyl]carbonylthio}-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;
155

 Methyl 5-[(3-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
160 3-pyridinecarboxylate;

Methyl 5-[(4-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

165 Methyl 5-[(2,3,5,6-Tetrafluorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(3,5-Di-t-butylphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

170 Methyl 5-[(1-Methylimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(1-Methyltetrazol-5-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

175

Methyl 5-[(5-Nitrobenzimidazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(4-(Trifluoromethoxy)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

180

Methyl 5-[(Quinolin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

185 Methyl 5-[(4-Bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

190 Methyl 5-[(Pentafluorophenyl)thiomethyl]-2-(difluoro-methyl)-4-(2-methylpropyl)-6-(trifluoro-methyl)-3-pyridinecarboxylate;

Methyl 5-[(2,5-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

195 Methyl 5-[(2,3,5,6-Tetrafluoro-4-(trifluoromethyl)phenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(4-Methylpyrimidin-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

200 Methyl 5-[(4-Nitrophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

205 Methyl 5-[(4-Methoxyphenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

210 Methyl 5-[(2,6-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(Quinolin-8-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

215 Methyl 5-[(Pyrimidin-2-yl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

Methyl 5-[(4-(Acetylamino)phenyl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
220 3-pyridinecarboxylate;

Methyl 5-[(Benzoxazol-2-yl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

Methyl 5-[(4-Bromo-2-(trifluoromethoxy)phenyl)
225 thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-
(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(3-Aminophenyl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

230 Methyl 5-[(2-Methoxyphenyl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

Methyl 5-[(5-Methylbenzimidazol-2-yl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
235 3-pyridinecarboxylate;

Methyl 5-[(Benzimidazol-2-yl)thiomethyl]-2-
(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

Methyl 5-[(3-Methoxyphenyl)thiomethyl]-2-
240 (difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-
3-pyridinecarboxylate;

Methyl 5-[(Benzothiazol-2-yl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

245 Methyl 5-[(3-Chlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(3,4-Dichlorophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

250

Methyl 5-[(2-Naphthyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(2-Pyridyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

255

Methyl 5-[(2-bromophenyl)thiomethyl]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

260 Bis{3-(carbomethoxy)-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-5-pyridyl}methyl Sulfide;

Methyl 5-[(2-Chloro-3,4-methylenedioxyphenyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

265

Methyl 5-[(2-pyridyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

270 Methyl 5-[(2-quinolinyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Methyl 5-[(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate; and

275 Methyl 5[(6-chloro-1,3-benzodioxan-8-yl)methylthio]-2-(difluoromethyl)-4-(2-methylpropyl)-6-(trifluoromethyl)-3-pyridinecarboxylate;

Diethyl 5,5'-(Carbonyldiimino)bis[6(difluoromethyl)-4-ethyl-2-(trifluoromethyl)-3-pyridinecarboxylate;

280 Methyl 2-(Difluoromethyl)-4-(2-methylpropyl)-5-[[[(dimethylamino)thiono]thiomethyl]-6-(trifluoromethyl)-3-pyridinecarboxylate;

285 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]carbonyl}pyridine;

290 2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]hydroxymethyl}pyridine;

2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]carbonyl}pyridine;

- 295 2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]fluoromethyl}pyridine;
- 2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]fluoromethyl}pyridine;
- 300 2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-(2-naphthylfluoromethyl)pyridine;
- 2-(Difluoromethyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]mercaptomethyl}pyridine;
- 305 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]mercaptomethyl}pyridine;
- 2-(Difluoromethyl)-5-hydroxymethyl-4-phenyl-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]mercaptomethyl}pyridine;
- 310 2-(Cyclopentyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]carbonyl}pyridine;
- 2-(1-Pyrrolidinyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]carbonyl}pyridine;
- 315 2-(1-Pyrrolidinyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]hydroxymethyl}pyridine; and
- 2-(1-Pyrrolidinyl)-5-hydroxymethyl-4-(4-fluorophenyl)-6-(trifluoromethyl)-3-{[4-(trifluoromethyl)phenyl]fluoromethyl}pyridine.
- 320

22. The compound of claim 14 wherein

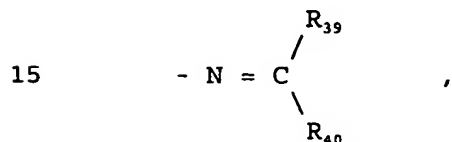
R_2 is selected from the group consisting of alkyl and fluorinated alkyl;

R_3 is selected from the group consisting of $-\text{CO}_2R_7$,
 5 wherein R_7 is selected from the group consisting of hydrogen and alkyl;

R_4 is selected from the group consisting of alkyl and thio;

R_5 is selected from the group consisting of
 10 heterocyclyl, arylthioalkyl, heteroarylthioalkyl,

$-\text{CO}_2R_{14}$,
 wherein R_{14} is alkyl;



wherein R_{39} is alkoxy, and
 R_{40} is haloalkyl;

20 $-\text{SR}_{45}$,
 wherein R_{45} is selected from the group consisting of hydrogen, $-\text{SR}_{46}$, and $-\text{CH}_2R_{47}$,

wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and

25 R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, naphthyl and benzodioxanyl; and

30
$$\begin{array}{c} \text{O} \\ || \\ - \text{S} - \text{C} - \text{R}_{50} \end{array},$$

 wherein R_{50} is selected from the group
 consisting of alkyl and alkoxy; and

R_6 is selected from the group consisting of alkyl and
fluorinated alkyl;

35 or a pharmaceutically acceptable salt or tautomer
 thereof,

 provided that when R_2 is trifluoromethyl, R_3 is
 CO_2CH_3 , R_4 is isobutyl, and R_5 is CO_2CH_3 , then R_6 is
 selected from the group consisting of alkyl comprising at
40 least two carbon atoms and fluorinated alkyl.

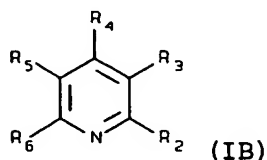
 23. A compound of claim 14 that is Dimethyl 5,5'-
 dithiobis[2-difluoromethyl]-4-(2-methylpropyl)-6-
 (trifluoromethyl)-3-pyridinecarboxylate].

 24. A pharmaceutical composition for the
 prophylaxis or treatment of a hyperlipidemic condition
 wherein the condition is atherosclerosis and the
 composition comprises an atherosclerotic amount of a
5 compound of Formula IA of claim 1 with a pharmaceutically
 acceptable carrier.

 25. A pharmaceutical composition for the
 prophylaxis or treatment of a hyperlipidemic condition
 wherein the condition is dislipidemia and the composition
 comprises a therapeutically effective amount of a
5 compound of Formula IA of claim 1 with a pharmaceutically
 acceptable carrier.

299

26. A method for inhibiting the activity of cholesteryl ester transfer protein *in vivo* by administering to a subject a therapeutically effective amount of a compound of Formula IB:



5

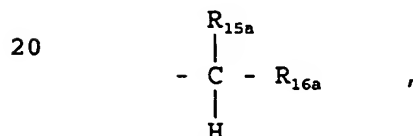
wherein:

R_2 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, alkyl, fluorinated alkyl, fluorinated aralkyl, chlorofluorinated alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, alkoxyalkyl, and alkoxycarbonyl; provided that at least one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of hydroxy, amido, arylcarbonyl, heteroarylcarbonyl, hydroxymethyl

-CHO,

-CO₂R₇, wherein R_7 is selected from the group consisting of hydrogen, alkyl and cyanoalkyl; and



wherein R_{15a} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy and heterocyclyloxy, and

25

30 R_{16a} is selected from the group consisting of
alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl,
haloalkynyl, aryl, heteroaryl, and heterocyclyl,
arylalkoxy, trialkylsilyloxy;

R_4 is selected from the group consisting of hydrogen,
hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl,
35 cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl,
cycloalkylalkyl, cycloalkenylalkyl, aralkyl,
heteroarylalkyl, heterocyclalkyl, cycloalkylalkenyl,
cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
heterocyclalkenyl, alkoxy, alkenoxy, alkynoxy, aryloxy,
40 heteroaryloxy, heterocyclloxy, alkanoyloxy, alkenoyloxy,
alkynoyloxy, aryloyloxy, heteroaryloxy,
heterocyclloxy, alkoxycarbonyl, alkenoxycarbonyl,
alkynoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl,
heterocyclloxycarbonyl, thio, alkylthio, alkenylthio,
45 alkynylthio, arylthio, heteroarylthio, heterocyclthio,
cycloalkylthio, cycloalkenylthio, alkylthioalkyl,
alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
heteroarylthioalkyl, heterocyclthioalkyl,
alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,
50 arylthioalkenyl, heteroarylthioalkenyl,
heterocyclthioalkenyl, alkylamino, alkenylamino,
alkynylamino, arylamino, heteroarylamino,
heterocycllamino, aryldialkylamino, diarylamino,
diheteroarylamino, alkylarylamine, alkylheteroarylamine,
55 arylheteroarylamine, trialkylsilyl, trialkenylsilyl,
triarylsilyl,

$-OC(O)N(R_{8a}R_{8b})$, wherein R_{8a} and R_{8b} are
independently selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl and
60 heterocyclyl,

$-SO_2R_9$, wherein R_9 is selected from the group
consisting of hydroxy, alkyl, alkenyl, alkynyl,
aryl, heteroaryl and heterocyclyl,

301

65 -OP(O) (OR_{10a}) (OR_{10b}), wherein R_{10a} and R_{10b} are
independently selected from the group consisting of
hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl,
heteroaryl and heterocyclyl, and

70 -OP(S) (OR_{11a}) (OR_{11b}), wherein R_{11a} and R_{11b} are
independently selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl and
heterocyclyl;

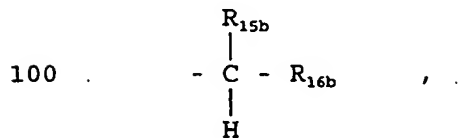
R₅ is selected from the group consisting of hydrogen,
hydroxy, halogen, alkyl, alkenyl, alkynyl, cycloalkyl,
cycloalkenyl, haloalkyl, haloalkenyl, haloalkynyl, aryl,
75 heteroaryl, heterocyclyl, alkoxy, alkenoxy, alkynoxy,
aryloxy, heteroaryloxy, heterocyclyoxy,
alkylcarbonyloxyalkyl, alkenylcarbonyloxyalkyl,
alkynylcarbonyloxyalkyl, arylcarbonyloxyalkyl,
heteroarylcarbonyloxyalkyl, heterocyclylcarbonyloxyalkyl,
80 cycloalkylalkyl, cycloalkenylalkyl, aralkyl,
heteroarylalkyl, heterocyclylalkyl, cycloalkylalkenyl,
cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
heterocyclylalkenyl, alkylthioalkyl, cycloalkylthioalkyl,
alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
85 heteroarylthioalkyl, heterocyclylthioalkyl,
alkylthioalkenyl, alkenylthioalkenyl, alkynylthioalkenyl,
arylthioalkenyl, heteroarylthioalkenyl,
heterocyclylthioalkenyl, alkoxyalkyl, alkenoxyalkyl,
alkynoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl,
90 heterocyclyoxyalkyl, alkoxyalkenyl, alkenoxyalkenyl,
alkynoxyalkenyl, aryloxyalkenyl, heteroaryloxyalkenyl,
heterocyclyoxyalkenyl, cyano,
hydroxymethyl,

-CO₂R₁₄,

95 wherein R₁₄ is selected from the group
consisting of alkyl, alkenyl, alkynyl, aryl,

302

heteroaryl and heterocyclyl;

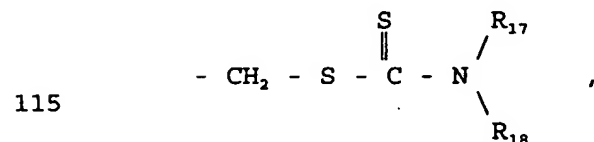


wherein R_{15b} is selected from the group consisting of hydroxy, hydrogen, halogen, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio, heterocyclylthio, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocycliloxy, aroyloxy, and alkylsulfonyloxy, and

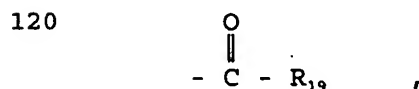
105

R_{16b} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, arylalkoxy, and trialkylsilyloxy;

110



wherein R_{17} and R_{18} are independently selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;



wherein R_{19} is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, $-SR_{20}$, $-OR_{21}$, and $-R_{22}CO_2R_{23}$, wherein

125

R_{20} is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aminoalkyl, aminoalkenyl, aminoalkynyl, aminoaryl, aminoheteroaryl, aminoheterocyclyl, alkylheteroarylamino,

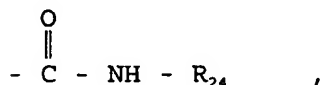
130

arylheteroarylamino,

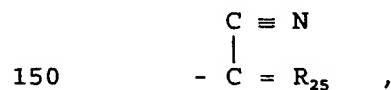
135 R_{21} is selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl,

R_{22} is selected from the group consisting of
alkylene or arylene, and

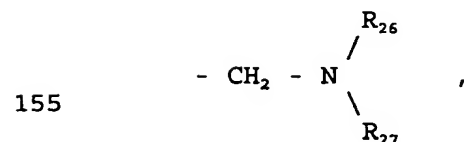
140 R_{23} is selected from the group consisting of
alkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl;



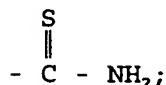
145 wherein R_{24} is selected from the group
consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl,
aralkenyl, and aralkynyl;



wherein R_{25} is heterocyclidenyl;

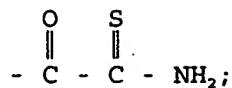


160 wherein R_{26} and R_{27} are independently selected
from the group consisting of hydrogen, alkyl,
cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and
heterocyclyl;

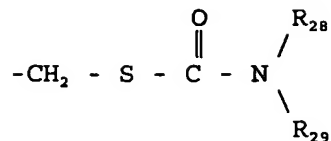


304

165



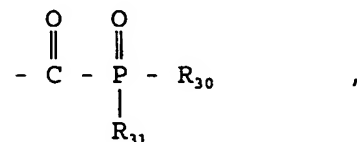
170



175

wherein R_{28} and R_{29} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

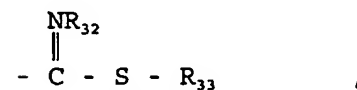
180



185

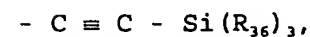
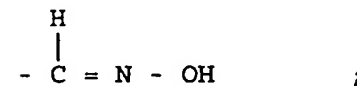
wherein R_{30} and R_{31} are independently alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, and heterocycloxy; and

190



wherein R_{32} and R_{33} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

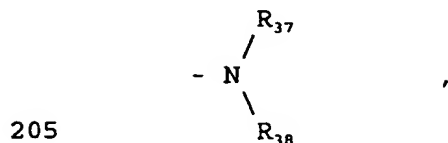
195



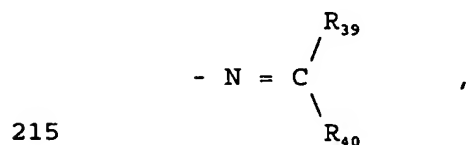
wherein R_{36} is selected from the group consisting of alkyl, alkenyl, aryl, heteroaryl and

305

200 heterocyclyl;

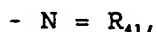


210 wherein R_{37} and R_{38} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, and heterocyclyl;

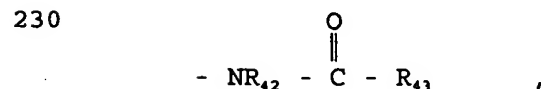


220 wherein R_{39} is selected from the group consisting of hydrogen, alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy, heterocyclyoxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio, and

225 R_{40} is selected from the group consisting of haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl, haloheterocyclyl, cycloalkyl, cycloalkenyl, heterocyclylalkoxy, heterocyclylalkenoxy, heterocyclylalkynoxy, alkylthio, alkenylthio, alkynylthio, arylthio, heteroarylthio and heterocyclylthio;



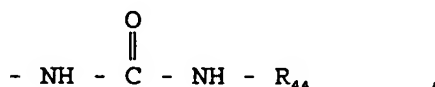
wherein R_{41} is heterocyclylidenyl;



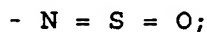
wherein R_{42} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl,

306

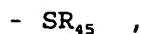
- 235 aryl, heteroaryl, and heterocyclyl, and
 R_{43} is selected from the group consisting of
hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl,
heterocyclyl, cycloalkyl, cycloalkenyl, haloalkyl,
haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl,
240 and haloheterocyclyl;



- wherein R_{44} is selected from the group
245 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
alkynyl, aryl, heteroaryl and heterocyclyl;



- 250 - N_3 ;



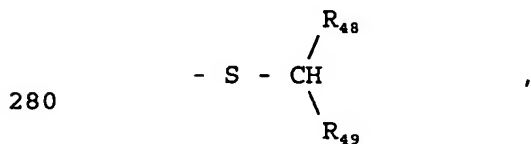
- wherein R_{45} is selected from the group
consisting of hydrogen, alkyl, alkenyl, alkynyl,
aryl, heteroaryl, heterocyclyl, haloalkyl,
255 haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl,
haloheterocyclyl, heterocyclyl, cycloalkylalkyl,
cycloalkenylalkyl, aralkyl, heteroarylalkyl,
heterocyclylalkyl, cycloalkylalkenyl,
cycloalkenylalkenyl, aralkenyl, heteroarylalkenyl,
260 heterocyclylalkenyl, alkylthioalkyl,
alkenylthioalkyl, alkynylthioalkyl, arylthioalkyl,
heteroarylthioalkyl, heterocyclylthioalkyl,
alkylthioalkenyl, alkenylthioalkenyl,

307

alkynylthioalkenyl, arylthioalkenyl,
 265 heteroarylthioalkenyl, heterocyclylthioalkenyl,
 aminocarbonylalkyl, aminocarbonylalkenyl,
 aminocarbonylalkynyl, aminocarbonylaryl,
 aminocarbonylheteroaryl, and
 aminocarbonylheterocyclyl,
 270 -SR₄₆, and -CH₂R₄₇,

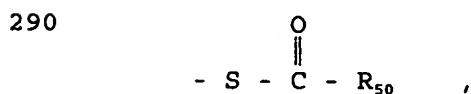
wherein R₄₆ is selected from the group
 consisting of alkyl, alkenyl, alkynyl, aryl,
 heteroaryl and heterocyclyl, and

R₄₇ is selected from the group consisting of
 275 hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl
 and heterocyclyl; and



wherein R₄₈ is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 alkynyl, aryl, heteroaryl and heterocyclyl, and

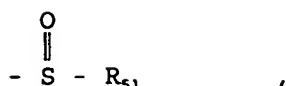
285 R₄₉ is selected from the group consisting of
 alkoxy, alkenoxy, alkynoxy, aryloxy, heteroaryloxy,
 heterocycliloxy, haloalkyl, haloalkenyl,
 haloalkynyl, haloaryl, haloheteroaryl and
 haloheterocyclyl;



wherein R₅₀ is selected from the group
 consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
 295 alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy,
 alkenoxy, alkynoxy, aryloxy, heteroaryloxy and
 heterocycliloxy;

308

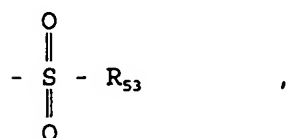
300



305

wherein $\text{R}_{\text{S}1}$ is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, haloheteroaryl and haloheterocyclyl; and

310



wherein $\text{R}_{\text{S}3}$ is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl;

315

or a pharmaceutically acceptable salt or tautomer thereof,

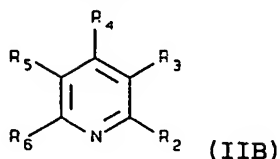
320

provided that when R_5 is selected from the group consisting of heterocyclylalkyl and heterocyclylalkenyl, the heterocyclyl radical of the corresponding heterocyclylalkyl or heterocyclylalkenyl is other than a δ -lactone; and

provided that when R_4 is aryl, heteroaryl or heterocyclyl, and one of R_2 and R_6 is trifluoromethyl, then the other of R_2 and R_6 is difluoromethyl.

309

27. A compound represented by the generic formula:



wherein:

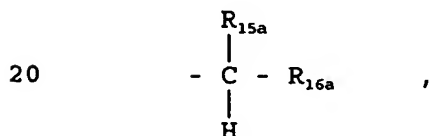
R_2 and R_6 are independently selected from the group
 5 consisting of hydrogen, hydroxy, alkyl, fluorinated
 alkyl, fluorinated aralkyl, chlorofluorinated alkyl,
 cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy,
 alkoxyalkyl, and alkoxycarbonyl; provided that at least
 10 one of R_2 and R_6 is fluorinated alkyl, chlorofluorinated
 alkyl or alkoxyalkyl;

R_3 is selected from the group consisting of
 arylcarbonyl, heteroarylcarbonyl, hydroxymethyl,
 arylalkoxyalkyl, trialkylsilyloxyalkyl,

-CHO,

15 -CO₂R₇,

wherein R_7 is selected from the group consisting
 of hydrogen and alkyl; and



wherein R_{15a} is selected from the group
 consisting of hydroxy, halogen, alkylthio and
 25 alkoxy, and

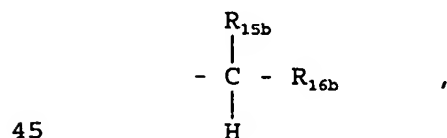
R_{16a} is selected from the group consisting of
 alkyl, haloalkyl, alkenyl, aryl and heteroaryl;

310

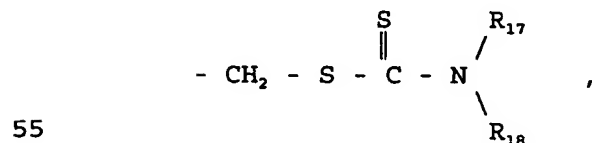
R_4 is selected from the group consisting of hydrogen, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, alkoxy, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl;

R_5 is selected from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, aralkyl, alkoxy, aryloxy, cycloalkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, alkoxyalkenyl, arylcarbonyloxyalkyl, pyrrolyl, substituted pyrrolidinyl, hydroxymethyl, arylalkoxyalkyl, and trialkylsilyloxyalkyl,

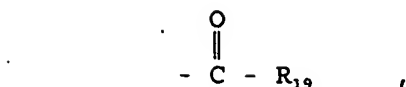
$-CO_2R_{14}$,
wherein R_{14} is alkyl;



wherein R_{15b} is selected from the group consisting of hydroxy, halogen, alkoxy, and alkylthio, aryloxy, and alkylsulfonyloxy, and R_{16b} is selected from the group consisting of alkyl, alkenyl, aryl, and heteroaryl;



wherein R_{17} and R_{18} are independently alkyl;



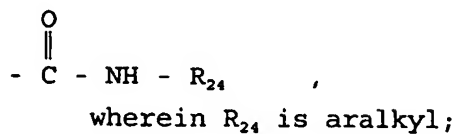
wherein R_{19} is aryl, heteroaryl, $-SR_{20}$, and $-OR_{21}$,

311

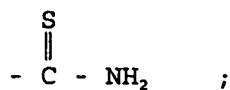
wherein R_{20} is selected from the group consisting of aryl, heteroaryl and aminoalkyl, and

R_{21} is selected from the group consisting of aryl and heteroaryl;

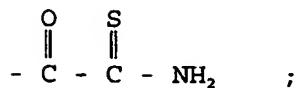
65



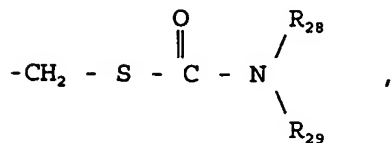
70



75

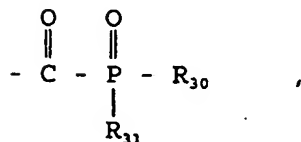


80

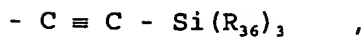


wherein R_{28} and R_{29} are independently alkyl;

85



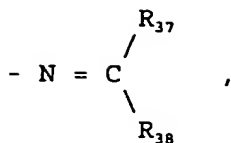
wherein R_{30} and R_{31} are independently alkoxy;



wherein R_{36} is alkyl;

312

90



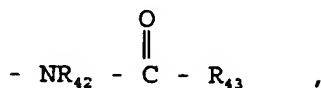
95

wherein R_{37} is selected from the group consisting of hydrogen, alkoxy, and alkylthio, and R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, heterocyclalkoxy, and alkylthio;

100

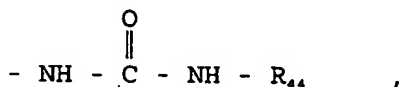
provided that when R_{37} is hydrogen, then R_{38} is selected from the group consisting of haloalkyl, cycloalkyl, and heterocyclalkoxy;

105



wherein R_{42} is selected from the group consisting of hydrogen and alkyl, and R_{43} is substituted heteroaryl;

110



wherein R_{44} is selected from the group consisting of aryl and heteroaryl;



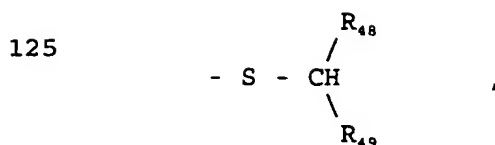
115

wherein R_{45} is selected from the group consisting of haloalkyl, heterocyclalkyl, alkylthioalkyl, aminocarbonylalkyl, $-SR_{46}$, and $-CH_2R_{47}$,

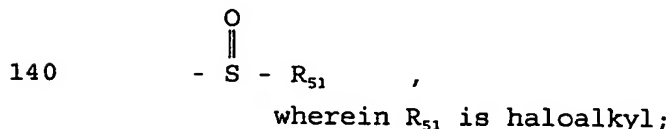
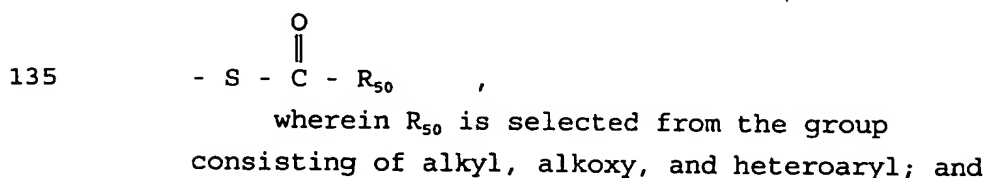
120

wherein R_{46} is selected from the group consisting of aryl and heteroaryl, and R_{47} is selected from the group consisting of methylenedioxyphenyl, pyridyl, quinolinyl, tetrahydronaphthyl and benzodioxanyl;

313



130 wherein R_{48} is selected from the group consisting of hydrogen and alkyl, and R_{49} is selected from the group consisting of alkoxy and haloalkyl;



or a pharmaceutically acceptable salt or tautomer thereof,

provided that:

145 when R_2 is selected from the group consisting of difluoromethyl and trifluoromethyl, R_3 is selected from the group consisting of $-CO_2H$, $-CO_2CH_3$, and $-CO_2C_2H_5$, R_5 is hydrogen, and R_6 is selected from the group consisting of hydrogen and trifluoromethyl, then R_4 is selected from the group consisting of cycloalkyl, cycloalkylalkyl, heteroarylalkyl, aralkenyl, alkoxy, thio, trialkylsilyl, alkylamino, and $-OC(O)N(R_8)_2$, wherein R_8 is aryl; provided further that when R_2 , R_3 and R_5 are as defined above, and R_4 is alkoxy, then R_6 is hydrogen;

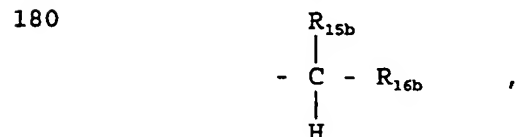
155 when R_2 is selected from the group consisting of

fluorinated methyl and chlorofluorinated methyl, R_3 is selected from the group consisting of hydroxymethyl and CO_2R_7 , R_5 is selected from the group consisting of hydroxymethyl and CO_2R_{14} , R_6 is selected from the group consisting of fluorinated methyl and chlorofluorinated methyl, and R_7 and R_{14} are independently alkyl, then R_4 is selected from the group consisting of thio, trialkylsilyl, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl;

when R_2 is difluoromethyl, R_3 is $-\text{CO}_2\text{C}_2\text{H}_5$, R_4 is hydrogen, R_5 is $-\text{CO}_2\text{C}_2\text{H}_5$, then R_6 is selected from the group consisting of hydrogen, monofluoroalkyl, difluoroalkyl and alkoxyalkyl;

when R_2 is trifluoromethyl, R_3 is $-\text{CO}_2R_7$, R_5 is methyl, R_6 is selected from the group consisting of fluorinated methyl, fluorinated ethyl and chlorofluorinated methyl, and R_7 is selected from the group consisting of hydrogen and alkyl, then R_4 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl;

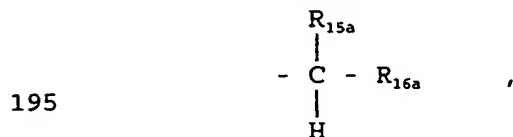
when R_4 is selected from the group consisting of alkyl, cycloalkyl and cycloalkylalkyl, R_3 is $-\text{CO}_2R_7$, and R_7 is alkyl, then R_5 is other than arylcarbonyl, heteroarylcarbonyl or



wherein R_{16b} is alkyl when R_{15b} is selected from the group consisting of hydroxy, halogen, alkylthio and alkoxy, or wherein R_{16b} is aryl or heteroaryl when R_{15b} is hydroxy;

when R_4 is selected from the group consisting of

alkyl, cycloalkyl and cycloalkylalkyl, R_5 is $-\text{CO}_2R_{14}$, and
 190 R_{14} is alkyl, then R_3 is other than arylcarbonyl,
 heteroarylcarbonyl or



wherein R_{16a} is alkyl when R_{15a} is selected from the group
 consisting of hydroxy, halogen, alkylthio and alkoxy, or
 wherein R_{16a} is aryl or heteroaryl when R_{15a} is hydroxy; and

200 when R_2 and R_6 are independently selected from
 fluorinated methyl and chlorofluorinated methyl, R_3 is
 CO_2R_7 , R_5 is hydroxy, alkoxy or aryloxy, then R_4 is
 selected from the group consisting of aryl, cycloalkyl,
 cycloalkylalkyl, heteroarylalkyl, thio, trialkylsilyl,
 205 alkylamino, and $-\text{OC}(\text{O})\text{N}(\text{R}_8)_2$, wherein R_8 is aryl; and

when R_4 is aryl and one of R_2 and R_6 is
 trifluoromethyl, then the other of R_2 and R_6 is
 difluoromethyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/01871

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D213/80 C07D213/81 C07D213/83 C07D409/12 C07D417/04 C07D413/04 C07D409/04 C07D407/04 C07D401/12 A61K31/44		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 04528 A (BAYER AG ;BAYER AG (US)) 5 February 1998 (1998-02-05) cited in the application see claim 11 and overlap when R5 = Aralkoxyalkyl ---	1-27
X	WO 92 20659 A (MONSANTO CO) 26 November 1992 (1992-11-26) see examples a, b and overlap when X = OH, Hal, SA1k, OA1k & US 5 169 432 A cited in the application --- -/--	14,27
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 16 July 1999		Date of mailing of the international search report 30/07/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Frelon, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/01871

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 11112 A (MONSANTO CO) 10 June 1993 (1993-06-10) see example B, page 6 and overlap when R3 = SAlk, OAlk & US 5 260 262 A cited in the application ---	14,27
X	EP 0 133 612 A (MONSANTO CO) 27 February 1985 (1985-02-27) see ex. 3,6,7,11-18,20-22,26-33,52-60,63,65-69,72, 75-77,84-87,96,97,109-116... and overlaps ---	14,27
X	EP 0 135 491 A (MONSANTO CO) 27 March 1985 (1985-03-27) examples 32-34 ---	14,27
X	EP 0 181 852 A (MONSANTO CO) 21 May 1986 (1986-05-21) see examples 3-6,8,10-14,16,17,35-37,39,66,67,70,71,77 and overlap & US 4 655 816 A cited in the application ---	14,27
X	EP 0 182 769 A (MONSANTO CO) 28 May 1986 (1986-05-28) see examples 2-8,12-19,21-24,43,49,58,60,63,76,77,89,12 1,122,126,127,132,175,188,195,198,204-211, 214,220,223,224,226-228 and overlap & US 4 698 093 A cited in the application ---	14,27
X	EP 0 245 230 A (MONSANTO CO) 11 November 1987 (1987-11-11) see overlap when Ra = Alk, Ar & US 4 936 905 A cited in the application ---	14,27
X	EP 0 252 055 A (MONSANTO CO) 7 January 1988 (1988-01-07) see examples 94,105,132,142,146,191,194 and overlap when X = N=CH-SAlk & US 4 885 026 A cited in the application ---	14,27
X	EP 0 276 204 A (MONSANTO CO) 27 July 1988 (1988-07-27) page 16; example 30 ---	14,27
	-/--	

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 99/01871

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 278 944 A (MONSANTO CO) 17 August 1988 (1988-08-17) see example 21 (intermed.) & US 4 988 384 A cited in the application ---	14,27
X	EP 0 278 945 A (MONSANTO CO) 17 August 1988 (1988-08-17) see prep. step 8; example 38 (step 1) ---	14,27
X	EP 0 435 843 A (MONSANTO CO) 3 July 1991 (1991-07-03) see prep. steps 4 and 8 & US 5 129 943 A cited in the application ---	14,27
X	US 5 125 956 A (KORTE DONALD E ET AL) 30 June 1992 (1992-06-30) see compounds 1-9, 11, 12, 14-16, 18, 19, 26, 29-31, 33, 34, 39, 40 , 44, 45, 47, 48, 53, 79, 81, 86, 91, 134, 135, 139 ---	14,27
X	WO 92 21674 A (MONSANTO CO) 10 December 1992 (1992-12-10) see examples a(3), a(4), e(2), e(3) & US 5 156 670 A cited in the application ---	14,27
X	LEN F. LEE ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 55, no. 9, 1990, pages 2872-2877, XP002109410 EASTON US examples 8-11 ---	14,27
X	LEN F. LEE ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 55, no. 9, 1990, pages 2964-2967, XP002109411 EASTON US examples 3, 4, 6, 7 ---	14,27
X	S.G. HEGDE: JOURNAL OF ORGANIC CHEMISTRY, vol. 56, no. 19, 1991, pages 5726-5729, XP002109412 EASTON US examples 1, 3-8 ---	14,27
A	EP 0 796 846 A (BAYER AG) 24 September 1997 (1997-09-24) page 12 - page 14 ---	1-27
A	EP 0 818 197 A (BAYER AG) 14 January 1998 (1998-01-14) abstract -----	1-27

INTERNATIONAL SEARCH REPORT

...ernational application No.

PCT/US 99/01871

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

The present claims relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely those compounds recited in the examples and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/01871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9804528 A	05-02-1998	AU 3897197 A HR 970425 A NO 990399 A	20-02-1998 31-08-1998 29-03-1999
WO 9220659 A	26-11-1992	US 5169432 A AT 151753 T AU 2156892 A CA 2102118 A DE 69219122 D EP 0586556 A ES 2102508 T JP 6509067 T	08-12-1992 15-05-1997 30-12-1992 24-11-1992 22-05-1997 16-03-1994 01-08-1997 13-10-1994
WO 9311112 A	10-06-1993	US 5260262 A AU 3221293 A CA 2122262 A EP 0621863 A JP 7502993 T US 5298479 A US 5380699 A	09-11-1993 28-06-1993 10-06-1993 02-11-1994 30-03-1995 29-03-1994 10-01-1995
EP 0133612 A	27-02-1985	US 4692184 A AR 240452 A AT 61048 T AU 564070 B AU 3177784 A BG 60364 B BR 8404011 A CA 1272199 A CY 1459 A DD 222767 A DK 385884 A,B, EG 17234 A FI 843169 A,B, GB 2145713 A,B GR 80080 A HK 4289 A IE 57473 B IN 158230 A JP 1756379 C JP 4047667 B JP 60078965 A KE 3834 A MW 1684 A MX 172742 B MX 14130 A MX 165160 B MX 165161 B OA 7791 A PT 79061 A,B RO 89518 A RO 94161 A TR 22859 A US 4826530 A US 5142055 A YU 140284 A ZM 5984 A ZW 12884 A	08-09-1987 30-04-1990 15-03-1991 30-07-1987 14-02-1985 30-09-1994 16-07-1985 31-07-1990 21-07-1989 29-05-1985 12-02-1985 30-08-1993 12-02-1985 03-04-1985 14-12-1984 27-01-1989 27-01-1993 27-09-1986 23-04-1993 04-08-1992 04-05-1985 02-12-1988 11-12-1985 11-01-1994 01-03-1993 29-10-1992 29-10-1992 20-11-1986 01-09-1984 30-06-1986 30-03-1988 16-09-1988 02-05-1989 25-08-1992 31-10-1987 21-01-1985 17-10-1984

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/01871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0133612 A		BG 60410 B US 4978384 A	28-02-1995 18-12-1990
EP 0135491 A	27-03-1985	AT 40262 T AU 566077 B AU 3181084 A BG 42832 A BG 48457 A BR 8404010 A CA 1269383 A CS 8406101 A CY 1425 A DD 231715 A DD 228247 A DK 385784 A FI 843168 A,B, GB 2145085 A,B GR 80077 A HK 30988 A IN 160125 A JP 1828435 C JP 60058961 A KE 3794 A MW 1584 A MX 13453 A OA 7790 A PT 79062 A,B RO 89127 A RO 93219 A SU 1565339 A SU 1577682 A SU 1531853 A TR 22217 A YU 140084 A ZM 5884 A ZW 12984 A AU 4165985 A	15-02-1989 08-10-1987 14-02-1985 15-02-1988 15-02-1991 16-07-1985 22-05-1990 15-07-1988 02-09-1988 08-01-1986 09-10-1985 12-02-1985 12-02-1985 20-03-1985 30-11-1984 06-05-1988 27-06-1987 15-03-1994 05-04-1985 11-03-1988 11-12-1985 01-02-1993 20-11-1986 01-09-1984 30-04-1986 31-12-1987 15-05-1990 07-07-1990 23-12-1989 06-10-1986 31-10-1987 21-01-1985 17-10-1984 07-11-1985
EP 0181852 A	21-05-1986	US 4655816 A AT 55991 T AU 576913 B AU 4933885 A JP 1937815 C JP 6067907 B JP 61148163 A	07-04-1987 15-09-1990 08-09-1988 15-05-1986 09-06-1995 31-08-1994 05-07-1987
EP 0182769 A	28-05-1986	US 4698093 A AT 55124 T AU 577164 B AU 4933785 A CA 1296007 A JP 1937814 C JP 6067906 B JP 61158965 A US 4835279 A US 4921530 A US 4797149 A	06-10-1987 15-08-1990 15-09-1988 15-05-1986 18-02-1992 09-06-1995 31-08-1994 18-07-1986 30-05-1989 01-05-1987 10-01-1989

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 99/01871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0245230 A	11-11-1987	AU 589522 B AU 7265687 A JP 62267266 A US 4936905 A	12-10-1989 12-11-1987 19-11-1987 26-06-1990
EP 0252055 A	07-01-1988	US 4885026 A AT 71940 T AU 591282 B AU 7268687 A DE 3776211 A GR 3003646 T JP 1873798 C JP 5087066 B JP 62273956 A US 5019153 A US 5196045 A	05-12-1989 15-02-1992 30-11-1989 19-11-1987 05-03-1992 16-03-1993 26-09-1994 15-12-1993 28-11-1987 28-05-1991 23-03-1993
EP 0276204 A	27-07-1988	DD 266955 A	19-04-1989
EP 0278944 A	17-08-1988	US 4988384 A AT 81124 T AU 604834 B AU 1137988 A BG 60044 A CA 1309405 A DD 267416 A DE 3874903 A DK 62288 A ES 2052779 T FI 880551 A,B, GR 3006621 T IE 63069 B JP 1932636 C JP 6060171 B JP 64000082 A OA 8713 A SU 1836015 A TR 23551 A US 5424274 A US 5773389 A US 5219824 A ZW 1788 A BG 60370 B US 5100461 A	29-01-1991 15-10-1992 03-01-1991 11-08-1988 16-08-1993 27-10-1992 03-05-1989 05-11-1992 16-08-1988 16-07-1994 10-08-1988 30-06-1993 22-03-1995 26-05-1995 10-08-1994 05-01-1989 31-03-1989 23-08-1993 01-03-1990 13-06-1991 30-06-1998 15-06-1993 08-06-1988 14-10-1994 31-03-1992
EP 0278945 A	17-08-1988	US 4826532 A AT 100806 T AU 597787 B AU 1138088 A BG 47193 A CZ 8800790 A DD 281950 A DE 3887357 D DE 3887357 T DK 62388 A FI 880552 A JP 2572099 B JP 63301866 A	02-05-1989 15-02-1994 07-06-1990 11-08-1988 15-05-1990 15-10-1997 29-08-1990 10-03-1994 26-05-1994 10-08-1988 10-08-1988 16-01-1997 08-12-1988

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/01871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0278945 A		OA 8712 A	31-03-1989
		SU 1814516 A	07-05-1993
		TR 23947 A	01-01-1989
		ZW 1688 A	11-05-1988
EP 0435843 A	03-07-1991	AT 107303 T	15-07-1994
		AU 624034 B	28-05-1992
		AU 6840290 A	01-08-1991
		CA 2033040 A	28-06-1991
		CN 1053428 A	31-07-1991
		DE 69009962 D	21-07-1994
		DE 69009962 T	15-12-1994
		DK 435843 T	04-07-1994
		ES 2025033 T	01-10-1994
		FI 906362 A	28-06-1991
		JP 8319285 A	03-12-1996
		JP 5320156 A	03-12-1993
		JP 7035380 B	19-04-1995
		OA 9338 A	15-09-1992
		US 5129943 A	14-07-1992
		ZM 5590 A	30-08-1991
		ZW 20390 A	19-06-1991
US 5125956 A	30-06-1992	AU 650116 B	09-06-1994
		AU 1461392 A	15-09-1992
		EP 0573575 A	15-12-1993
		JP 6505022 T	09-06-1994
		US 5391540 A	21-02-1995
		WO 9214711 A	03-09-1992
		US 5512536 A	30-04-1996
		US 5643854 A	01-07-1997
		US 5843867 A	01-12-1998
		US 5877119 A	02-03-1999
		US 5824625 A	20-10-1998
		US 5228897 A	20-07-1993
WO 9221674 A	10-12-1992	US 5156670 A	20-10-1992
		AU 647289 B	17-03-1994
		AU 1999492 A	08-01-1993
		CA 2102698 A	04-12-1992
		EP 0641337 A	08-03-1995
		JP 6508358 T	22-09-1994
EP 0796846 A	24-09-1997	DE 19610932 A	25-09-1997
		AU 1628097 A	25-09-1997
		BG 101339 A	30-04-1998
		BR 9701348 A	10-11-1998
		CA 2200175 A	20-09-1997
		CZ 9700843 A	15-10-1997
		HR 970105 A	30-04-1998
		JP 9255574 A	30-09-1997
		NO 971269 A	22-09-1997
		NZ 314419 A	23-12-1998
		PL 319050 A	29-09-1997
		SG 50805 A	20-07-1998
		SK 36197 A	05-11-1997
EP 0818197 A	14-01-1998	DE 19627431 A	15-01-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/01871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0818197 A		BG 101748 A	30-04-1998
		BR 9703890 A	03-11-1998
		CA 2209825 A	08-01-1998
		CN 1174196 A	25-02-1998
		CZ 9702144 A	14-01-1998
		HR 970333 A	30-04-1998
		HU 9701157 A	30-03-1998
		JP 10167967 A	23-06-1998
		NO 973143 A	09-01-1998
		PL 320953 A	19-01-1998
		SG 46781 A	20-02-1998
		SK 92597 A	06-05-1998